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Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy

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Abstract

Objectives—To determine the incidence, clinical manifestations and risk factors for immune reconstitution inflammatory syndrome (IRIS) in young children initiating highly active antiretroviral therapy (HAART).

Design—A prospective cohort of antiretroviral-naïve HIV-infected children less than 24 months of age enrolled in a treatment strategies trial in Johannesburg, South Africa.

Methods—Among 169 HIV-infected children initiating HAART, April 2005 to November 2006, the records of 83 children suspected to have IRIS within 6 months of starting treatment were reviewed to determine whether they met criteria for IRIS. Seven were excluded due to incomplete follow-up. Pretreatment and post-treatment characteristics of children with and without IRIS were compared.

Results—Overall, 34/162 (21%) children developed IRIS at a median of 16 days (range 7–115 days) post-HAART initiation. Bacille Calmette-Guérin reaction was most common occurring in 24/34 (71%) children, primarily injection site lesions and/or ipsilateral axillary lymphadenitis with abscess. Other IRIS conditions (not mutually exclusive) included *Mycobacterium tuberculosis* ($n = 12$), cytomegalovirus pneumonia ($n = 1$), *Streptococcus pneumoniae* sepsis ($n = 1$), and severe seborrheic dermatitis ($n = 1$). Children with IRIS were younger (median age 7 vs. 10 months, $P = 0.007$) with a lower CD4 cell percentage (median 13.9 vs. 19.2, $P = 0.009$) at HAART initiation than controls. After 24 weeks on HAART, 62% of IRIS cases vs. 28% of controls had HIV RNA more than 400 copies/ml ($P = 0.001$), odds ratio = 2.88 (95% confidence interval = 1.14–7.29) after adjusting for baseline factors.

Conclusion—Infants and young children with advanced HIV disease initiating HAART are at high risk for developing IRIS, leading to additional morbidity and possibly impairing virologic response to antiretroviral treatment.

Keywords

immune reconstitution inflammatory syndrome; pediatric HAART; pediatric HIV

Introduction

With increased availability of highly active antiretroviral treatment (HAART) in high HIV prevalence, resource-constrained settings, immune reconstitution inflammatory syndrome (IRIS) has been recognized as a significant complication of treatment initiation [1–7]. It is estimated that 10–32% of adults starting HAART will develop IRIS, an exacerbation or atypical presentation of opportunistic infections associated with immune recovery, within 6 months of starting treatment [1,2,8–11]. Although the number of children worldwide initiating HAART has increased substantially, there are limited data about IRIS in infants and children starting HAART [6,7,12–14]. This issue is of particular importance in Sub-Saharan Africa where tuberculosis is common, Bacille Calmette-Guérin (BCG) vaccination is routinely administered at birth, and more than 600 000 children are estimated to be in urgent need of HAART [13, 15].

In a study of 153 children with advanced HIV disease initiating HAART as part of Thailand's national treatment program (median age 7.9 years), the incidence of IRIS was found to be 19% [6]. The IRIS events included mycobacterial disease (44%), Varicella Zoster, Herpes Simplex, and *Cryptococcus neoformans* infections, and median time to IRIS onset was 4 weeks. Low CD4 cell percentage was a risk factor for developing IRIS [6]. In Cape Town, South Africa, 11 new, recurrent or worsening *Mycobacterium tuberculosis* (TB) events were reported among children initiating HAART over a 2-year period [7]. Similar to the Thai study, the children studied were older and generally developed IRIS symptoms within the first months of treatment.

BCG vaccination, using a live-attenuated form of *Mycobacterium bovis*, is routinely administered to newborns in sub-Saharan Africa to prevent severe forms of the disease. Concerns have been raised that BCG vaccination poses a risk to HIV-infected infants [16–18]. Hesselink *et al.* [17] reported 25 children in the Western Cape Province, South Africa, diagnosed with BCG disease [17]. Seventeen of these children were HIV-infected and four were characterized as having IRIS reactions. In a recent report of 373 HIV-infected children initiating HAART as part of a clinical trial in South Africa, 33 (8.8%) developed BCG-associated IRIS at a median age of 4 months and a median of 4 weeks after treatment initiation [14].

In addition to increased morbidity, treatment of IRIS-related conditions can complicate HAART. In particular, cotreatment of TB is especially complex in young children because of interactions between nevirapine and rifampin. Efavirenz cannot be substituted for nevirapine, as dosing has not yet been determined for children less than 3 years of age. Although international guidelines suggest antiretroviral treatment with three nucleoside reverse transcriptase inhibitors (NRTI) when using rifampin [19], in practice South African clinicians either use ritonavir or higher doses of lopinavir–ritonavir with two NRTI [20,21]. Furthermore, the efficacy of HAART in infants receiving treatment for IRIS-related conditions, particularly for TB, has not been described.

This report describes the incidence, risk factors and characteristics of IRIS among a cohort of HIV-infected children less than 2 years of age initiating HAART as part of a clinical trial in Johannesburg, South Africa. We also compare virologic, immunologic and clinical outcomes after 6 months of HAART between children with and without IRIS.

Methods

Study population

HAART-naïve HIV-infected infants less than 24 months of age who were exposed to nevirapine for prevention of mother-to-child transmission were enrolled into a clinical trial of HAART strategies, between April 2005 and November 2006 at Coronation Hospital in Johannesburg, South Africa (clinicaltrials.gov NCT00117728). Children were referred from inpatient wards and pediatric HIV clinics at Coronation and Chris Hani Baragwanath hospitals as well as from nearby HIV clinics. HIV infection was documented with at least one positive test using DNA PCR or at least one HIV RNA viral load more than 5000 copies/ml. The parent or legal guardian of each child provided written informed consent and the study was approved by the Institutional Review Boards of Columbia University and the University of the Witwatersrand.

Treatment and monitoring

Children were eligible for HAART if they had WHO stage III or IV disease, or CD4 cell% less than 25% in children less than 12 months or less than 20% in children less than 35 months, or had recurrent (>2/year) or prolonged (>4 weeks) hospitalization for HIV-related infections. Children requiring acute treatment for opportunistic infections or tumors were excluded with the exception of children requiring treatment for TB. Severe liver dysfunction evidenced by elevated alanine aminotransferase precluded HAART initiation. Children were initiated on a regimen of lopinavir/ritonavir, lamivudine (3TC) and stavudine (d4T). Dosing was determined using body surface area and was recalculated at each study visit. Ritonavir was substituted for lopinavir/ritonavir in children aged less than 6 months or those who were receiving concomitant treatment with rifampin.

HIV RNA viral load (Roche Diagnostics, Branchburg, New Jersey, USA) was measured at treatment initiation, and weeks 12 and 24 post-treatment. CD4 cell counts and percents were measured at treatment initiation and at week 24. Children were examined by a study physician every 4 weeks. Physicians were available between visits to address acute problems and families were encouraged to use the study clinic for all of their children's medical needs. Caretakers were counseled regarding medication administration and adherence was reviewed through structured questionnaires and measurement of unused medications. Laboratory and clinical data were collected at each visit and maintained in an electronic database.

Immune reconstitution inflammatory syndrome case definition

At each visit, study physicians who had received clinical training in likely presentation of IRIS in children evaluated and recorded whether there were signs and symptoms consistent with IRIS. The records of all children flagged as 'suspect IRIS' by study physicians within the first 24 weeks of treatment were retrospectively reviewed by an independent member of the research team who was not directly involved in patient care. In addition, the records of all children who died, who initiated TB treatment, or who had been hospitalized and treated with antimicrobials during the first 24 weeks of treatment were also reviewed. All study documents, as well as all available clinic and hospital records, were reviewed.

We adapted the definition of IRIS used by Puthanakit *et al.* [6]. Children meeting any of the following criteria were classified as 'IRIS' cases: new symptomatic presentation of infections

with pathogens previously reported to be associated with IRIS in the adult or pediatric literature; new reaction to BCG; reemergence or exacerbation of TB; exacerbation of prior condition, for example, dermatitis. Given the complexity of TB diagnosis in young children, the diagnosis was based on overall clinical picture and clinician decision to initiate TB treatment [22]. Microscopy, culture, biopsy and radiography results were recorded when available. Standard treatment for TB in South Africa is rifampin, isoniazid and pyrazinamide for 2 months followed by 4 months of rifampin and isoniazid. All newborns in South Africa routinely receive intradermal Danish strain BCG vaccination (Statens Serum Institute, Copenhagen, Denmark). Recommended treatment for BCG disease is rifampin, isoniazid and ethionamide. For children already receiving TB treatment, ethionamide is added to the regimen.

All children whose records were not reviewed, as well as those who were reviewed but did not meet IRIS case definition, were classified as controls. Surviving children who did not complete at least 12 weeks of follow-up (lost-to-follow-up, withdrawn, or transferred out) were excluded.

Statistical analysis

Pretreatment and post-treatment characteristics of IRIS cases and controls were compared using chi-squared tests for categorical variables or Fisher's exact test if expected cell sizes were less than five, *t*-tests for normally distributed continuous variables and Wilcoxon tests for nonnormal continuous variables. The child's weight was expressed as the sex and age-adjusted Z-score [23]. Laboratory values were included if they were done within 6 weeks of scheduled visits. Multivariable analysis was conducted using logistic regression and SAS statistical software (Cary, North Carolina, USA) and variables were included in the final model if associated with the outcome ($P < 0.05$) or if their inclusion modified the association between IRIS and the outcome by more than 10%.

Results

Incidence of immune reconstitution inflammatory syndrome

A total of 169 HIV-infected children were initiated on HAART between April 2005 and November 2006. Fifty-one percent were male and the median age was 8 months (range 2–24 months) with 31% initiating treatment less than 6 months of age.

The records of 83 (49.1%) children were reviewed as possible IRIS cases (Fig. 1). Of these, 34 met IRIS case definition. Seven children not followed to 12 weeks were excluded. Thus, of 162 HIV-infected children who initiated HAART and were retained in care for more than 12 weeks, 34 (21.0%) developed IRIS within the first 24 weeks of treatment.

Profile of immune reconstitution inflammatory syndrome cases

Table 1 describes the clinical manifestations of children who met study criteria for IRIS. The median time to first symptom presentation following HAART was 16 days [range 7–115 days, interquartile range (IQR) = 13–53 days], with 73.5% manifesting symptoms within 30 days. BCG-related complications were the most frequent IRIS manifestations occurring in 24/34 (70.6%) children with IRIS, that is, 24/162 (14.8%) of the treatment cohort. Median time to first symptom from treatment initiation was 14 days (IQR = 12–27) among children with BCG-related IRIS vs. 54 days (IQR = 18–84) for other IRIS conditions; median age at start of treatment was 6 months (IQR = 4–9) for the BCG IRIS group and 9 months (IQR = 6–11) for the other IRIS cases.

Three children had local injection site lesions, 15 children had BCG disease involving the regional lymph nodes and/or other local lesions primarily ipsilateral axillary lymphadenitis with abscess formation, five children had both regional and local lesions, and one child was

diagnosed with probable disseminated TB/BCGosis. One child was already receiving BCG treatment but developed an enlarged, suppurative right axillary node 4 weeks after HAART initiation. Six children who developed BCG disease were also newly diagnosed with TB, including the child diagnosed with disseminated infection who died and two who were already on TB treatment when BCG symptoms developed. Overall, 11 children had abscess aspirations and two children required surgical incision and drainage. Six samples sent to the laboratory were smear positive for acid-fast bacilli and three yielded positive cultures for *M. tuberculosis* complex. The majority of children, 17/24 (70.8%), received treatment for BCG disease (including the child who continued on previously prescribed therapy).

It was difficult to clearly identify children with TB-related IRIS because of nonspecific presentation (cough, fevers, respiratory distress, gastrointestinal complaints and failure-to-thrive) and inconsistent implementation of diagnostic protocols (five children had abnormal chest radiograph consistent with TB and four were documented as Mantoux test positive). Overall, twelve children were newly treated for TB including six children with concomitant BCG disease.

Other IRIS manifestations included cytomegalovirus pneumonia, *Streptococcus pneumoniae* sepsis with empyema, severe herpes labialis and acute, severe worsening of seborrheic dermatitis with bacterial superinfection requiring hospitalization. One child already receiving TB treatment at HAART initiation was hospitalized for fever, cough, respiratory distress and hypoxemia, developed concomitant BCG-related complications while hospitalized and was discharged with a diagnosis of *Pneumocystis pneumonia* and BCGosis.

Three of 34 (8.8%) children who developed IRIS died: two children with localized BCG disease and one child with disseminated BCG and TB. There were 14 deaths among 128 (10.9%) controls ($P = 1.0$).

Risk factors for immune reconstitution inflammatory syndrome

Univariable risk factors for IRIS are displayed in Table 2. Children who developed IRIS were significantly younger at treatment initiation than controls, median age 7 months (range 2–18 months) vs. 10 months (range 2–24 months), $P = 0.007$. WHO stage was similar between groups, but children with IRIS had significantly lower pretreatment CD4 cell percents. Children with IRIS had higher pretreatment HIV RNA levels and lower sex-adjusted and age-adjusted weight-for-age Z-scores than controls, for example, 82% of children with IRIS were less than -2 SD below the mean compared with 49% of controls, $P = 0.0005$. There was a trend towards less cotreatment for TB at the time of HAART initiation among children with IRIS but this association was not significant.

In multivariable analysis, young age at treatment initiation, low pretreatment CD4 cell% and low weight-for-age were each independently associated with developing IRIS. In a model including these variables: age less than 6 months [odds ratio (OR) = 4.41; 95% confidence interval (CI) = 1.73–11.24], CD4 cell% less than 10 vs. more than 10 (OR = 5.45; 95% CI = 1.87–15.93), and weight-for-age Z-score less than -2 (OR = 4.19; 95% CI = 1.56–11.24) were associated with increased risk of developing IRIS.

Immunologic, clinical and virologic responses to HAART

Immunologic, clinical and virologic responses to HAART at 24 weeks were compared between children in the IRIS and control groups (Table 3). After 24 weeks of HAART, mean CD4 cell % remained significantly lower in the IRIS group compared with controls (21.8 vs. 29.6, $P = 0.0001$) but the mean change in CD4 cell% was similar (mean increase from pretreatment to 24 weeks of 7.8 and 9.0 CD4 cell% point for IRIS vs. controls, respectively). Similarly, at 24

weeks, the mean Z-score for the IRIS group remained lower than the control group (-1.76 vs. -0.68 , $P = 0.0029$) but the mean change over time in weight-for-age Z-scores was similar across groups.

At 24 weeks post-HAART initiation, there were a significantly greater proportion of children in the IRIS group who had not suppressed: of children who had developed IRIS, 62% had a viral load more than 400 copies/ml at 24 weeks compared with 28% of controls ($P = 0.001$) (Table 3). There remained a significantly higher rate of failure in the IRIS group compared with the controls if exclusions and deaths were counted as failures. A nonsignificant trend in the same direction was seen at 12 weeks. Because viral loads more than 750 000 copies/ml were not further quantified and the majority of children had high pretreatment viral loads, we were unable to accurately evaluate the magnitude of change from baseline.

The lower rates of viral suppression at 24 weeks among children who had developed IRIS were not explained by age or by their severity of disease pretreatment as measured by pretreatment viral load, CD4 cell%, weight-for-age Z-score and clinical stage. In a multivariable model, only IRIS status was significantly associated with lack of viral suppression. If weight-for-age Z-score and pretreatment viral load were included in the model, IRIS remained significantly associated with a reduced likelihood of achieving viral suppression less than 400 copies/ml at 24 weeks (OR = 2.88 95% CI = 1.14–7.29) (Table 4). We included these two factors as they slightly attenuated the association between IRIS and lack of viral suppression. Inclusion of any of the other pretreatment characteristics had no effect.

Discussion

Despite its clinical importance, IRIS has not been well studied in children. This is the first report to describe the incidence of and risk factors for IRIS in a cohort of infants and young children less than 24 months of age initiating HAART. Approximately 21% of these children met criteria for IRIS and, similar to findings in cohorts of older children and adults, children with advanced immune suppression were at higher risk for developing the syndrome than those with a less severe disease profile [1,3–6,9,11,14]. We also determined that younger age at HAART initiation was associated with increased risk for IRIS. Intriguingly, our results suggest that children with IRIS may be less likely to suppress HIV after 6 months of HAART than those without the syndrome.

Diagnosis of IRIS in children is complex due to a lack of standard definitions and diagnostic dilemmas associated with several other infectious and pulmonary conditions in young children, particularly TB [22]. BCG-related IRIS was the most common diagnosis in our cohort perhaps due in part to the ease of diagnosis: 14.8% of all children starting HAART were diagnosed with a BCG-related complication. This is far higher than the incidence rate of 2% for vaccine site abscesses and 0.7% for lymphadenitis reported in a Thai study of older children [16] and higher than that reported in another cohort of infants 6–12 weeks of age enrolled in a HAART strategies trial in South Africa in which 8.8% were reported to have developed BCG regional IRIS [14,24]. It has been pointed out that BCG vaccination poses a significant risk to HIV-infected infants [17,18]. In our cohort, morbidity associated with BCG IRIS was substantial. Three deaths occurred: one in a child with presumed disseminated BCG and TB, and two in children with localized disease (not thought to be related to the children's deaths). Furthermore, the majority of children required single or repeated abscess aspirations or surgical incision and drainage as well as new medication in addition to their already complex regimens. Recent WHO guidelines discourage BCG for HIV-infected children [25]. However, as the vaccine is routinely given prior to knowledge of the child's HIV status, this recommendation has little practical utility. The high rate of BCG-related complications experienced by young HIV-infected children initiating HAART in our study supports recent recommendations for careful

monitoring of HIV-infected BCG vaccinated infants particularly during the immediate period following HAART initiation [25].

Twelve of the 34 IRIS cases were attributed to TB, including six with BCG comorbidity. TB is notoriously difficult to diagnose in infants and we relied on TB treatment as confirmation of the diagnosis [22]. For some children, medical records provided further evidence supporting the diagnosis, including tuberculin skin tests, radiographs and bacteriologic cultures. The overwhelming predominance of BCG-related and TB-related causes of IRIS in young children suggests that further investigation of prophylaxis with anti-TB drugs and other approaches to decrease the risk of TB exposure and acquisition are warranted.

The median time to IRIS symptoms was 16 days. This is somewhat shorter than reported from Thailand, but may be explained by our focus on the first 6 months of treatment compared with 48 weeks of observation in the Thai study [6] or to the younger age of our cohort. We also found that lower CD4 cell%; younger age and lower weight-for-age Z-score pretreatment were each associated with a significantly higher risk for developing IRIS. Children less than 6 months of age were four-times more likely to be diagnosed with IRIS than older children, whereas CD4 cell% less than 10 was associated with a more than five-fold increase over higher CD4 cell%. Advanced disease has been associated with IRIS in adult and pediatric populations but age has not been previously identified as a risk factor [1,3,4,6,9,11,14].

The association between young age and increased risk for IRIS could pose significant challenges in light of new recommendations to initiate HAART in all HIV-infected children less than 1 year of age, regardless of clinical or immunologic status [26]. It is possible that early initiation of HAART prior to disease progression may decrease the risk for IRIS. This might explain the lower rates of BCG IRIS observed in the treatment strategy trial mentioned earlier [14]. As all children in our study had evidence of advanced HIV disease to meet enrollment criteria, we could not tease out the relationships between age, disease stage, and the development of IRIS. It will be critically important, therefore, to monitor rates and manifestations of IRIS as more infants initiate HAART early in TB endemic areas with routine newborn BCG vaccination.

After 24 weeks of treatment, mean CD4 cell% and weight-for-age Z-scores in the IRIS group remained lower than the control group, but mean increases over time for both CD4 cell% and weight were similar between groups [27,28]. In contrast, children with IRIS were significantly less likely to achieve viral suppression to less than 400 copies/ml by 24 weeks than controls. We adjusted for markers of disease severity at HAART initiation (CD4 cell%, viral load categories, weight-for-age, WHO stage, age, etc.) but these markers did not account for the difference in response rate. However, these parameters only partially capture the full spectrum of the severity of disease and residual confounding may account for the reduced viral suppression. In particular, we were unable to determine the actual viral load value pretreatment when the reported value was more than 750 000 copies/ml and therefore could not adequately adjust for pretreatment viral load. Our finding may represent the longer time needed to achieve complete viral suppression when pretreatment viral load is very high [29,30]. Also, as the IRIS-defining conditions that we identified almost all required TB treatment, we are concerned about possible drug-drug interactions. Several studies have identified pharmacokinetic interactions between rifampin and ritonavir as well as ritonavir boosted protease inhibitors that may result in sub-therapeutic antiretroviral drug levels [21,31–35]. In addition, the burdens of acute illness and concomitant medications for treatment of IRIS conditions are likely to result in adherence challenges that may impact HAART efficacy. One study of adherence in young South African children identified ritonavir treatment as a risk factor for incomplete adherence and lower rates of complete viral suppression [36].

There are several limitations to this study. IRIS is difficult to diagnose in children secondary to the lack of a standard definition and the well known dilemmas of diagnosing TB and other infectious diseases [22]. We chose to use the IRIS definition used in a previous study of children and to rely, to a large extent, on study physician diagnosis [6]. Although the suspected IRIS cases were determined prospectively during the study, a review of these cases occurred retrospectively by only one independent reviewer. We recognize that classification of some of the cases may not be entirely accurate. Given the difficulties of distinguishing disseminated BCG disease from TB, it is possible that some of the children listed as experiencing both complications were experiencing only disseminated BCG disease. This study was also limited by losses in both groups due to death and withdrawal. Given the lack of clinical detail surrounding deaths (several children died at home) as well as the severity of symptomatic disease pretreatment, it is possible that IRIS may have gone undetected and that the rate and severity of IRIS manifestations may have been underestimated.

In summary, in this cohort of infants and young children initiating HAART, IRIS was a common complication associated with significant morbidity, particularly in the youngest children with advanced HIV disease. Given the continuing large-scale rollout of HAART to infants and children in the developing world, careful monitoring is warranted following the initiation of therapy. Further research is needed to better predict and diagnose IRIS and the underlying infections associated with the syndrome and to determine best practices for prevention and treatment. In areas where BCG vaccination is routine, it will be critically important to continue to examine the consequences of vaccine policy for HIV-infected children.

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Fig. 1. Classification of 169 children initiating highly active antiretroviral treatment, November 2005 to April 2006, as immune reconstitution inflammatory syndrome (IRIS) or controls

*Children were flagged as 'suspect IRIS' by study clinicians. All 'suspect IRIS' cases as well as all deaths, hospitalizations, tuberculosis cases and children treated with antimicrobials were reviewed by study investigators.

Table 1

Clinical manifestation, diagnostic evaluations, treatment, diagnosis and outcomes for 34 infants and young children with immune reconstitution inflammatory syndrome following initiation of highly active antiretroviral therapy.

Case#	First symptoms	First symptoms	Clinical manifestations	Diagnostic evaluation	Diagnosis	Treatment	Outcome
	Age (months)	Days on HAART					
BCG-related complications							
1	2.7	12	Injection site abscess	Clinical diagnosis	Local BCG disease	None	A
2	2.9	15	Injection site abscess	Abscess aspiration AFB smear positive AFB culture positive for MTB complex	Local BCG disease	None	A
3	3	7	R axillary abscess	Abscess aspiration AFB smear negative AFB culture positive for MTB complex	Regional BCG disease	BCG treatment	A
4	3.3	14	R axillary abscess	Abscess aspiration AFB smear positive AFB culture negative	Regional BCG disease	BCG treatment	A
5	4.6	16	Suppurative R axillary node Injection site inflammation	Clinical diagnosis	Regional and local BCG disease	BCG treatment	A
6	5	28	R axillary abscess Injection site abscess	Abscess aspiration AFB smear positive AFB culture positive for MTB complex	Regional and local BCG disease	BCG treatment	A
7	5	29	R axillary abscess Multiple abscesses R axilla Abscesses R posterior shoulder	Axillary abscess aspiration Surgical incision and drainage AFB smear positive AFB culture negative	Regional BCG disease	BCG treatment	A
8	5.2	17	Suppurative R axillary node Injection site ulceration	Clinical diagnosis	Regional and local BCG disease	BCG treatment	A
9	5.6	13	R axillary abscess	Clinical diagnosis	Regional BCG disease	None	D
10	7	18	R axillary abscess	Clinical diagnosis	Regional BCG disease	BCG treatment	D
11	8.5	27	Suppurative R axillary node Injection site ulceration	Clinical diagnosis	Regional and local BCG disease	BCG treatment	A
12	10.2	28	Acute enlargement and suppuration of R axillary node*	Clinical diagnosis	Regional BCG disease	BCG treatment continued*	A
13	10.8	75	R axillary abscess	Abscess aspiration	Regional BCG disease	BCG treatment	A
14	13.9	53	R axillary adenitis	Clinical diagnosis	Regional BCG disease	None	A

Case#	First symptoms	First symptoms	Clinical manifestations	Diagnostic evaluation	Diagnosis	Treatment	Outcome
15	16.6	14	Suppurative R axillary node	Clinical diagnosis	Regional BCG disease	None	A
16	19.7	54	R axillary abscess **	Abscess aspiration AFB smear positive AFB culture negative	Regional BCG disease	BCG treatment (E added to TB regimen)	
BCG with other complications including TB							
1	5.4	16	Injection site abscess Postauricular abscess	Clinical diagnosis Postauricular abscess aspiration Culture positive for <i>Streptococcus pneumoniae</i>	Local BCG disease Bacterial abscess	None	A
2	5.9	9	Fevers, cough, GI symptoms Enlarged R axillary node R supraclavicular abscess	Hospitalization Mantoux (PPD) positive Abscess aspiration AFB smear negative AFB culture negative CXR – no results available	Pulmonary TB Regional BCG disease	TB treatment BCG treatment (E added to TB treatment)	A
3	6	11	Cough, fevers, mild respiratory distress	CXR: R upper lobe consolidation, bilateral hilar adenopathy TB bactec negative	Pulmonary TB	TB treatment	A
4	6	13	Enlarged (10 × 10 mm) R axillary node Cough, respiratory distress	Incision and drainage Hospitalization CXR: bilateral perihilar thickening, patchy upper lobe consolidation, mediastinal adenopathy Mantoux (PPD) positive	Regional BCG disease Pulmonary TB	BCG treatment TB treatment	A
5	8	13	Enlarged R axillary node Pneumonia	Clinical diagnosis Culture positive for MTB complex	Regional BCG disease Disseminated TB/BCGosis	BCG treatment	D
6	8.7	7	R axillary abscess Coughing poor response to antibiotics Mother treated for pulmonary TB	Abscess aspiration Clinical diagnosis	Regional BCG disease Pulmonary TB	BCG treatment TB treatment	A
7	9.2	13	Fevers, cough, failure-to-thrive	CXR: no results available TB Bactec negative Incision and drainage Multiple abscess aspirations AFB smear positive X2 AFB culture not available	Pulmonary TB Regional BCG disease	TB treatment BCG treatment (E added to TB treatment)	A
8	9.4	12	Fever, cough, respiratory distress, hypoxemia ***	Hospitalization	<i>Pneumocystis carinii</i> pneumonia	PCP treatment	A

Case#	First symptoms	First symptoms	Clinical manifestations	Diagnostic evaluation	Diagnosis	Treatment	Outcome
TB infection							
1	6.5	23	Enlarged R axillary node Injection site inflammation and suppuration Multiple satellite lesions	Clinical diagnosis Hospitalization CXR: R consolidation Mantoux (PPD) positive prior to HAART	Regional and local BCG disease Pulmonary TB	BCG treatment TB treatment	 A
2	7.5	115	History not available, diagnosed at another health facility	Hospitalization Clinical improvement with TB treatment	Pulmonary TB	TB treatment	A
3	9.9	54	Cough $\times$ 2 months	Clinical diagnosis Mantoux (PPD) positive >15 mm	Pulmonary TB	TB treatment	A
4	11.4	14	Cough, failure-to-thrive	Hospitalization CXR: negative TB Bactec negative	Pulmonary TB	TB treatment	A
5	11.8	18	Cough, fever, respiratory symptoms	Hospitalization CXR: multilobar pneumonia	Pulmonary TB	TB treatment	A
6	20.2	84	Cough, fever, weakness, hx of untreated TB	CXR: suspicious for TB	Pulmonary TB	TB treatment	A
Other complications							
1	4.9	9	Fevers, cough, respiratory distress, hypoxemia	Hospitalization Positive urine CMV antigen	CMV pneumonitis	Gancyclovir	A
2	12.3	84	Cough, fever, respiratory distress	Hospitalization Blood culture positive <i>Streptococcus pneumoniae</i>	Bacterial sepsis with empyema	Antibiotics	A
3	11.4	112	Severe worsening seborrheic Dermatitis with bacterial infection	Hospitalization Clinical diagnosis	Severe seborrheic dermatitis	Skin care Antibiotics	A
4	16.9	54	Herpes labialis**	Clinical diagnosis	Herpes labialis	Acyclovir	A

ART, antiretroviral therapy; BCG, Bacille Calmette-Guérin; E, ethambutol; IRIS, immune reconstitution inflammatory syndrome; TB, tuberculosis.

* Child on BCG treatment prior to initiation of HAART.

** Child on TB treatment prior to initiation of HAART.

Table 2

Pretreatment characteristics of HIV-infected children who developed immune reconstitution inflammatory syndrome and those who did not following initiation of highly active antiretroviral therapy.

	IRIS	No IRIS	P
N	34	128	
Sex			
Male	21 (62%)	62 (48%)	0.1670
Female	13 (38%)	66 (52%)	
Age at treatment initiation			
<6 m	16 (47%)	32 (25%)	0.0189
6–12 m	13 (38%)	53 (41%)	
12–18 m	5 (15%)	23 (18%)	
18–24 m	0	20 (16%)	
Median age (IQR) in months	7 (5–9)	10 (6–15)	0.007
Mean absolute CD4 (SD)	741 (753)	1075 (688)	0.0148
CD4 cell%			
<10	11 (32%)	14 (11%)	0.0086
10–14.9	9 (27%)	30 (23%)	
15–19.9	2 (6%)	24 (19%)	
≥20	12 (35%)	60 (47%)	
Median (IQR)	13.95 (9.2–22.1)	19.2 (13.5–24.8)	0.009
Viral load *			
<100 000	1 (3%)	12 (10%)	0.0440
100 000–749 999	6 (18%)	42 (35%)	
>750 000 copies/ml	26 (79%)	66 (55%)	
WHO stage			
I	5 (15%)	19 (15%)	0.5740
II	1 (3%)	10 (8%)	
III	15 (44%)	63 (49%)	
IV	13 (38%)	36 (28%)	
Weight-for-age (Z-score)			
Mean (SD)	−3.26 (1.68)	−2.09 (1.68)	0.0004
< −2 SD	28 (82%)	63 (49%)	0.0005
< −1 SD	31 (91%)	98 (77%)	0.06
Receiving TB treatment at or shortly before treatment initiation	3 (9%)	27 (21%)	0.1365
Initial regimen			
Ritonavir	18 (53%)	53 (41%)	0.2282
Lopinavir/ritonavir	16 (47%)	75 (59%)	

IRIS, immune reconstitution inflammatory syndrome.

* One child in the IRIS group and eight in the controls were missing their pretreatment viral load measurement for several reasons including blood not collected, sample insufficient, laboratory error, incorrect requisition form.

Table 3

Post-treatment characteristics of HIV-infected children who developed immune reconstitution inflammatory syndrome and those who did not.

	IRIS	No IRIS	<i>P</i>
<i>N</i>	34	128	
Deaths			
< 12 weeks	1	11	
12 to 24 weeks	2	3	
Viral load (copies/ml) at 12 weeks			
<50	1 (3%)	3 (3%)	
50–400	9 (29%)	53 (45%)	
>400	21 (68%)	61 (52%)	0.1957
Viral load (copies/ml) at 24 weeks *			
< 50	4 (14%)	48 (44%)	
50–400	7 (24%)	31 (28%)	
>400	18 (62%)	30 (28%)	0.0011
CD4 percentage at 24 weeks *			
<i>N</i> with CD4% at 24 weeks	29	110	
Mean	21.79	29.55	0.0001
Mean change (from time 0)	7.83	9.02	0.5149
CD4 percentage at 24 weeks			
<10	3 (10%)	1 (1%)	
10–14.9	6 (21%)	8 (7%)	
15–19.9	3 (10%)	10 (9%)	
≥20	17 (59%)	91 (83%)	0.0057
Weight-for-age (Z-score) at 12 weeks			
<i>N</i> with weight at 12 weeks	31	115	
Mean	−2.44	−1.15	0.0018
Mean change (from time 0)	0.82	0.78	0.8572
Weight-for-age (Z-score) at 24 weeks			
<i>N</i> with weight at 24 weeks	29	108	
Mean	−1.76	−0.68	0.0029
Mean change (from time 0)	1.64	1.20	0.0649

IRIS, immune reconstitution inflammatory syndrome.

* Two children in the IRIS and five children in the control group were missing viral load measurements at 24 weeks.

Associations between failure to achieve viral suppression at 24 weeks post-antiretroviral treatment initiation and pre-treatment characteristics and IRIS.

Table 4

	N	N (%)	VL >400 at 24 weeks	Univariable OR (95% CI)	P	Multivariate* OR (95% CI)	P
VL pre-treatment							
<750 000	58	17 (29%)				Ref	
≥750 000 copies/ml	71	30 (42%)		1.77 (0.85–3.68)	0.1303	1.41 (0.65–3.05)	0.3892
Weight-for-age							
<–2 STD	75	32 (43%)		2.19 (1.06–4.53)		1.54 (0.69–3.43)	
≥ –2 STD	63	16 (25%)			0.0355	Ref	0.2901
IRIS status							
IRIS case	29	18 (62%)		4.31 (1.82–10.18)		2.88 (1.14–7.29)	
Control	109	30 (28%)			0.0009	Ref	0.0259

IRIS, immune reconstitution inflammatory syndrome; STD, sexually-transmitted disease.

* Only variables associated with viral suppression or which modified the magnitude of the IRIS coefficient were included in the multivariable model.