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Pediatric HIV Immune Reconstitution Inflammatory Syndrome (IRIS)

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Summary

Purpose of Review—Little is known regarding HIV immune reconstitution inflammatory syndrome (IRIS) in children. As the ART roll out has gathered pace since 2004 in resource limited settings, pediatric IRIS has emerged as a clinical challenge.

Recent Findings—The incidence of IRIS appears to be between 10-20%. The commonest causes are mostly mycobacterial, including tuberculosis, atypical mycobacteria and BCG-related. However, in many pediatric cohorts, a marked early mortality within the first 90 days of antiretroviral therapy (ART) occurs. This mortality is poorly understood, and the contribution of IRIS to this mortality is unknown.

Summary—Children after starting ART may have paradoxical worsening of previously treated opportunistic infections. However due to the differences in children's immunology with vertical HIV transmission, children are likely at greater risk of unmasking occult, subclinical infections during immune reconstitution.

Keywords

HIV; AIDS; HAART; Children; Immune Reconstitution Inflammatory Syndrome

Introduction

Of the 2.5 million children living with HIV, about 780,000 were estimated to be in need of antiretroviral therapy and barely 115,500 children had access to treatment by the end of 2006, representing a coverage rate of about 15%, a 50% increase from the previous year [1]. Consequently, data on HIV immune reconstitution inflammatory syndrome (IRIS) in a pediatric population remains limited to case reports and small cohorts originating from resource limited settings.

Immune recovery usually occurs rapidly in HIV-infected children who initiate HIV antiretroviral therapy (ART). While the majority of children and adolescents experience profound benefit from ART, a subset clinically worsen with the recovery of their immune

systems. This IRIS is the occurrence of a paradoxical infectious or inflammatory condition in a patient recovering from severe immune deficiency.

In most instances, the etiology of IRIS is infectious. Two clinical scenarios commonly occur (Table 1) [2-4*]. One form is classified as “unmasking” IRIS, in which there is an underlying subclinical, previously unrecognized infection, which flares after starting ART. The other form is described as a paradoxical type, in which there is an exacerbation of a past known, often treated infection.

Mortality in resource-limited settings appears to be particularly high during the first few months after the start of ART. In several cohort of children between 76% and 90% of deaths occurred during the first 6 months of treatment [5,6]. In a large cohort from Zambia, the 90 days mortality rate was 17.4 per 100 child years, compared to 2.9 per 100 child years post 90 days [7]. In one study of Thailand, invasive bacterial disease, such as pneumonia and sepsis are reported to be frequent causes of death [8**]. It has not been established whether this early mortality is linked to only advanced HIV disease as many children start ART late in the disease [5,9] or whether some deaths are a result of IRIS.

The cause of IRIS is not well understood but is thought to be immunologically mediated occurring as a consequence of the recovery of specific immune responses to an underlying pathogen or antigen. In HIV infection it is temporally related to the initiation of ART and occurs in patients with severe baseline immune suppression [10]. Risk factors for IRIS include a high pathogen load and very low CD4 T-cell count when ART is initiated [8,11*]. Usually IRIS events occur in the presence of a rising CD4 T-cell count; however a systemic CD4 increase is not necessary for IRIS to occur.

IRIS Epidemiology in Children

Information about the incidence and spectrum of IRIS in children is limited. The majority of published pediatric IRIS work originates from Thailand. The incidence rate of IRIS in children ranges from 11.5 to 19.0 % in children commencing ART [12**,13]. Recent reports from Thailand by Puthanakit et al [8,11*,12**] have described IRIS in 153 symptomatic HIV-infected children in advanced stages (CD4 lymphocyte percentage $\leq$ 15%). After initiation of ART, the incidence of IRIS was 19% with a median onset of 4 weeks after ART initiation, but occurred as early as 2 weeks and as late as 31 weeks. Nearly 50% (14/32) were associated with mycobacterial organisms, including non-tuberculous mycobacterial (NTM) infection, followed by herpes viruses.

Although IRIS in children in Thailand was typically occurring in “older” children with severe immunosuppression (owing to delayed initiation of ART), it can occur in young infants and children who start therapy in accordance with World Health Organization (WHO) guidelines. IRIS events resolve spontaneously in a majority of cases, but can be fatal, especially in the younger children.

Case Definition

Though IRIS has diverse manifestations, there has been an attempt to outline a consensus case definition (Table 2) to enable further study of the condition. At present, there are no confirmatory tests for IRIS, and IRIS remains a diagnosis of exclusion.

Common Clinical IRIS Events in Pediatric Populations

Mycobacteria are by far the most common pathogens associated with IRIS in HIV-infected patients [14-18]. In the ART era, IRIS associated with *Mycobacterium tuberculosis* (TB) is

common in high TB prevalence areas, occurring in approximately 11-36% cases. Other infections e.g. varicella zoster, herpes simplex, meningeal cryptococcosis, and intestinal parasites have been associated with IRIS events. While the majority of IRIS events are infectious in nature, autoimmune IRIS reactions have also been described in adults [19].

Mycobacterium tuberculosis IRIS

In regions with a high prevalence of TB, children carry 10% of the overall TB burden [20, 21]. In addition, there is a high prevalence of HIV-1 infection among children with clinical and culture-confirmed TB in Africa, varying from 13 to 70% [22]. TB mortality in HIV infected children is much higher (24%) compared to HIV negative children (4%) [22]. In a recent cohort study reported from South Africa, the absolute incidence rate of TB-IRIS was 3.4% [23]. In Uganda, unmasking of TB occurred in 6.2% of children starting ART with the highest risk in the first 100 days of ART [24].

TB-IRIS can have a variety of diverse, clinical manifestations. Table 3 presents the clinical criteria of the infectious or inflammatory signs and symptoms needed for diagnosis of paradoxical TB IRIS. Risk factors in adults appear to be related to CD4 count, duration of antecedent TB therapy prior to initiating ART, and extrapulmonary TB have been described as a risk factor in adults [25]. In South African children, risk factors included malnutrition, severe CD4 depletion, WHO clinical stage III and IV, and history of TB [12**].

Non tuberculous mycobacterial IRIS

In a Thai cohort of 153 children, there were 7 cases of unmasking of previously unrecognized NTM infections and 2 cases of paradoxically worsening [11*]. The clinical presentation included fever, dyspnea, abdominal pain and subcutaneous nodules or suppurative lymphadenitis. The causative species were *Mycobacterium avium* complex, *M. kansasii*, *M. simae*. At the time the diagnosis of IRIS was made, NTM could be cultured from all 7 patients with unmasking type of IRIS but none of the 2 with paradoxical reaction. In adults, case reports have reported NTM unmasking IRIS events in persons with dramatically higher CD4 counts than traditionally associated with NTM.

Bacille Calmette Guérin (BCG) IRIS

BCG reactivation, presenting as local localized abscess, lymphadenopathy with or without systemic illness [Figure 1], has been reported in children previously vaccinated children after initiation ART in children from Ethiopia and Thailand [12,26-29]. A recent study from South Africa estimated the risk of disseminated BCG disease several hundred fold higher in HIV-infected infants compared to the documented risk in HIV-uninfected infants. The estimated risk range for HIV-infected infants to develop disseminated BCG disease was between 110 and 417/100,000 vaccine recipients, given a 95% BCG coverage, an HIV prevalence of 12.4-15.4% amongst women and a mother to child transmission rate between 5 and 15% [30]. In contrast, in a study from Thailand, the risk of IRIS due to BCG were 2% for vaccine site abscess and 0.7% for lymphadenitis in HIV infected children treated with ART [27]. BCG disease should be considered in HIV-infected infants with axillary adenitis ipsilateral to the vaccination site.

Skin manifestations of IRIS

Little information exists on how ARVs affect the course of skin disease in HIV infected children. In one retrospective observational study, HIV infected children exposed to ART showed a decrease in both inflammatory as infectious skin manifestations, underlining the reduction of morbidity of children successfully treated with ART [31]. However, the authors did not look at the incidence of skin manifestations following the start of ART.

In adults, dermatologic manifestations of IRIS are the most frequent [32], and this is likely true in children. In an unpublished 100 child cohort from Kwazulu-Natal, Dr. Van der Linden and colleagues found 58% had a new onset rash after starting ART. Frequently observed pathologies included: Molluscum (8%), Tinea capitis (20%), warts (16%), impetigo (12%), herpes zoster (5%), and other fungal rashes (24%). These dermatopathologies occur frequently during immune reconstitution, yet the relationship to IRIS is as yet unclear.

Herpes Zoster

Tangsinmankong et al. reported herpes zoster in 7 of 63 children as an IRIS complication [13]. In this report, 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 herpes zoster in conjunction with ART [13].

IRIS Pathogenesis

The pathogenesis of IRIS and nature of immune reaction to intracellular pathogens such as TB are not well understood [33-35], and may differ in children as compared to adults. In children with vertical HIV infection, it can be speculated that immaturity of immune mechanisms or severe immunosuppression owing to HIV may preclude the development of a typical T-cell specific immune response to a pathogen at the time of initial infection. Following initiation of ART, the recovery of pathogen-specific immunity in the face of the high antigenic burden accumulated during the period of immunosuppression could lead to an inflammatory response and result in the immune-mediated syndrome known as IRIS (Table 1). The “unmasking” of an infection is likely to be a more common cause for IRIS in young children infected with HIV perinatally as compared to adolescents and adults infected with HIV later in life by horizontal transmission, who would be more likely candidates to develop the “paradoxical” type of IRIS. In the latter scenario, amplification of pre-existing immunologic memory following immunologic recovery in the presence of a significant antigenic burden could elicit a severe inflammatory reaction resulting in IRIS. Possibly, the susceptibility of very young severely immunocompromised infants to adverse events including sepsis and even unexplained death following start of ART could be explained on this basis as a form of IRIS, but definitive evidence is lacking.

One potential way to understand which mechanism is involved would be to investigate in a research setting for evidence of immunologic memory to the IRIS- inciting pathogen prior to initiation of ART. The absence of pre-existing memory could be more supportive of an unmasking type of response, although the dilemma of new infection versus pre-existing infection would still need to be addressed. Interestingly, newborns develop BCG-specific T cell responses following BCG vaccination [34] and immunosuppressed HIV-infected children restore antimycobacterial immune responses upon receipt of HAART [36]. Development of immunologic memory in infants is likely to vary with different pathogens, and thus influence whether the IRIS is of the “unmasking” or “paradoxical” type.

Functional T helper (TH) cells classified as Interferon- γ (IFN- γ) producing TH1 and interleukin (IL)-4 producing TH2 cells have long been known to be important mediators of host defense. Recently, the discovery of TH17, a new lineage of helper T cells has provided new insights into immunoregulation. TH17 cells preferentially produce IL-17, IL-17F, and IL-22 as signature cytokines, and appear to play a critical role in sustaining inflammatory responses [37,38]. The relationship between TH subsets and factors that regulate predominance of one TH subset over another continue to evolve. A major cellular compartment responsible for mediating immunoregulatory functions is comprised by regulatory T-cells (T-regs) [39]. A reciprocal relationship has been described in the mouse between T-regs and TH17 cells,

through action of cytokines such as TGF- β , which in concert with IL-6, preferentially induces TH17 cells and in the absence of IL-6, favors T reg cell induction. The situation in humans is less well characterized, and differences between children and adults are poorly understood.

The predominant host defense against extracellular pathogens such as TB is mediated by TH1 cells. HIV infection is known to infect and deplete CD4 T-cells including T-regs. Following initiation of potent antiretroviral therapy, it is possible that there is rapid recovery of pathogen-specific TH1 cells, including those directed at intercurrent infectious organisms such as TB, and that reconstitution of T-regs is slower. In this situation, an IRIS event could be attributed to an exaggerated, uncontrolled inflammatory immune response of TH1 cells in the absence or deficiency of the normal physiological T-cell regulatory control mechanisms limiting the immune response. Thus, exaggerated inflammatory process could be triggered by even low frequencies of reconstituted antigen-specific TH1 cells following ART initiation. The lack of regulatory T-cell control may be due to a quantitative or qualitative deficiency of classical T-regs (CD4⁺ CD25⁺ FoxP3⁺) or of other types of regulatory T-cells, such as IL-10 producing CD4 T-cells. An imbalance of regulatory T cells could thus lead to dysregulated cytokine production with increases in production of cytokines such as IFN- γ and decreases in cytokines such as IL-10 by CD4 T-cells, increased immune activation, and increased antigen-specific proliferative response of T-cells. However, in the case of TB, the few available data in adults suggest that the reconstitution of detectable TB-specific TH1 cells progresses more slowly than the sometimes precipitous development of IRIS [40,41], suggesting that other mechanisms may be operative as well. In this context, besides the role of IFN γ production by TH1 cells which is key to limiting primary infection, the TH17 cells that produce IL-22, IL-23 and IL-17 are known to be important for recall responses in producing an accelerated memory response [42,43*]. Thus excessive TH17 cells could further contribute to the cytokine imbalance in favour of pro-inflammatory signals, through activity of innate and adaptive immune responses. These hypotheses need to be tested. Representative sampling of T-cells remains a challenge in understanding the immunology of IRIS, as what is occurring in peripheral blood versus in tissue may be different. Polymorphisms of genes encoding pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α have also been implicated in IRIS pathogenesis [44].

Many questions about pathogenesis of IRIS remain, and well-designed clinical studies coupled with laboratory investigations in HIV-infected children who develop IRIS are required. One study currently in development by the IMPAACT group is aimed to study pathogenesis of IRIS in HIV-infected children initiating ART (P1073).

IRIS in Resource-Limited Regions

In the past few years, ART therapy has become much more widely available in many resource limited regions of the world, including Sub-Saharan Africa and parts of Asia. As a result, IRIS is emerging as an important complication of HIV therapy in resource limited regions. Because of the limited availability of antiretroviral medications to date and parents tend to present the children late for treatment, often only children with the most advanced disease are treated, and thus at risk for developing IRIS. Children in resource-poor regions are at particularly high risk because of the high prevalence of infections that are associated with IRIS, including invasive bacterial, mycobacterial, fungal and parasitic infections.

Additionally, in children, underlying malnutrition and subsequent refeeding syndrome also can contribute to IRIS [45-47]. In resource-limited areas, bacterial infections and sepsis were frequent complications after starting HAART [8]. In malnourished children, C-reactive protein (CRP) levels have been shown to be predictive of latent infections before refeeding [45*]. This may be an important area of investigation as to whether CRP may be predictive of unmasking

IRIS. It is important to perform clinical research in these regions to determine the magnitude of the IRIS problem and to identify the best evidence-based management strategies.

Treatment of Unmasking IRIS

Treatment toward an unmasked opportunistic infection is generally the same. At this time, there are no data to suggest otherwise; however an unanswered question is whether shorter treatment durations can safely be given in the presence of a robust immune recovery. At present most clinicians err on the side of caution; however when treatments are toxic, expensive, or unavailable, close observation with shorter courses may be sufficient when coupled with a robust CD4 response in an otherwise non-toxic, hemodynamically stable, well child or adolescent. Unmasking events can be quite dramatic and may benefit from concomitant anti-inflammatory therapy, and occasionally when severe IRIS occurs temporary discontinuation of ART may at times be required.

Enhanced screening for occult infections, such as TB, prior to beginning ART has been shown to reduce the unmasking of infections. In one study from Uganda, TST screening pre-ART reduced unmasking of TB by >50%, although high rates of anergy (67%) existed in children with CD4% <10% [24]. For anergic children in TB high prevalence regions, screening chest x-rays may be warranted.

Treatment of Paradoxical IRIS

IRIS treatment is based primarily on adjunct anti-inflammatory measures (Table 4). However, in the largest case series of pediatric IRIS cases from Thailand, the most common causes for hospitalization were bacterial pneumonia in 62% and IRIS in 23% during the first 6 months of ART. Thus, one must consider bacterial infections, and in rapidly deteriorating children empiric antibiotics are warranted [8]. Diagnosis of IRIS and excluding alternative infectious diagnoses remain the most significant challenges. Anti-inflammatory therapy in the presence of an untreated infection or drug resistance is dangerous.

No randomized controlled trials have evaluated treatment of IRIS. Anecdotal experiences have used different therapeutic strategies depending on the severity of disease (Table 3). For mild cases, observation alone with close clinical and appropriate laboratory monitoring may suffice. For moderate cases of inflammation, non-steroidal anti-inflammatory drugs (NSAIDs) have been effective at successfully ameliorating symptoms [48]. For severe cases, several strategies have been employed. Corticosteroids, such as dexamethasone, have been utilized [48,49]. For IRIS induced lymphadenopathy, such as is common with TB IRIS, debulking the antigenic burden via lymph node drainage may be a viable diagnostic and therapeutic approach [49]. In episodes of culture negative cryptococcal meningitis IRIS, a combination of mechanical drainage via repeat lumbar punctures for alleviation of elevated intracranial pressure and corticosteroids have been used [49,50].

Reports in the literature show that corticosteroids have been used to treat IRIS, but there have been no randomized controlled trials. The WHO has recommended prednisone (1–2 mg/kg for 1–2 weeks, then gradually decreasing doses) for TB IRIS when severe paradoxical reactions occur; however, the WHO also indicates no evidence supports this [51,52]. Corticosteroids are not without risk. One such risk in resource limited regions is strongyloides hyperinfection [53].

The concept of prophylaxis to prevent IRIS is purely speculative at present. However, if the incidence of IRIS for common opportunistic infections, such as TB, is prospectively found to be in the range of 10-30%, prophylaxis during the first three to six months of ART is an obvious next step. A prophylactic agent would need to have the necessary properties of being an anti-

inflammatory with excellent tolerability and without any drug-drug interactions so as not to interfere with ART compliance or effectiveness.

Alternative Therapies and Future Possibilities

Alternative therapeutic approaches may include using thalidomide, chloroquine, or leflunomide for IRIS treatment or prophylaxis. Experience with these agents is negligible, and further investigation is warranted; however, each agent has properties making them an attractive potential alternative to corticosteroids. The key is however to understand the pathogenesis of IRIS which will allow the selection of rational therapy for proper, randomized controlled trials.

Conclusion

IRIS occurs in children; however little is known about IRIS in general, and minimal research has been performed in children and adolescents. Unmasking of occult infections appears to frequent complication in the first few months of ART.

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Picture courtesy of Dr. Dimitri Van der Linden

Figure 1.
Example of BCG-lymphadenitis as an IRIS event occurring child shortly after starting HIV antiretroviral therapy.

Table 1
Common Scenarios of HIV Immune Reconstitution Inflammatory Syndrome (IRIS)

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- “Unmasking” IRIS
 - Occult, subclinical opportunistic infection
 - Unmasked by immune recovery following ART initiation
 - Infectious pathogen typically detectable
 - “Paradoxical” IRIS
 - Clinical recrudescence of a successfully treated infection
 - Symptomatic relapse despite initial clinical improvement and continued microbiologic treatment success.
 - Antigen driven immune activation, often with a robust immune response in the setting of few or no detectable organisms.
 - Culture may be sterile due to effective opportunistic infection treatment
-

Table 2
Case Definition: Consensus Criteria for Diagnosis of Pediatric IRIS

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1	Evidence of clinical response to ART with: a. Virologic response with $>1 \log_{10}$ copies/mL decrease in HIV RNA (if possible).¹
2	Clinical deterioration from an infectious or inflammatory condition temporally related to the initiation of ART a. Unmasking IRIS requires a new active diagnosis² b. For Paradoxical TB-IRIS, refer to Table 3 for clinical criteria
3	Symptoms cannot be explained by: a. An alternate infection or neoplasm b. Treatment failure of the opportunistic infection.³ c. Adverse drug reaction d. Complete non-compliance to ART or TB treatment⁴
-

¹ IRIS can occur in the absence of a meaningful rise in CD4 count. In ART naïve persons, an initial virologic response generally always occurs. In non-naïve persons or with known ART resistance, proof of virologic response becomes more important.

² Unmasking caveats:

- Active infections, such as TB, should be excluded at time of ART initiation.
- Diagnosis of incident TB infections should conform to national or WHO guidelines. In children, bacteriologic confirmation may not always be achieved.
- “Unmasked” incident infections may have accelerated presentations with exaggerated symptoms.
- Refeeding syndrome of malnourished children may contribute to unmasking opportunistic infections [45*].
- Generally occurs within 6 months after ART initiation.

³ Paradoxical IRIS can occur with MDR and XDR TB; however, the primary concern is the efficacy of the TB therapy. For TB-IRIS, non compliance and TB treatment failure are critical to exclude.

⁴ Even with imperfect ART compliance and lack of HIV virologic suppression, immunologic reconstitution and CD4 rise can occur temporarily.

Table 3
Infectious or Inflammatory Clinical Criteria for Paradoxical TB-IRIS

Clinical Criteria:

At least 1 major clinical criterion or 2 minor clinical criteria are required:

Major criteria

1. New or enlarging lymph nodes, fistulas, cold abscesses, or other focal tissue involvement.
2. New or worsening radiological features of TB
3. New or worsening central nervous system TB (meningitis or focal neurological deficit).
4. New or worsening TB serositis (pleural effusion, ascites, or pericardial effusion) or arthritis.
5. Signs of tuberculin hypersensitivity (e.g. phlyctenular conjunctivitis, erythema nodosum).

Minor criteria

1. New or worsening constitutional symptoms such as fever, night sweats or weight loss.
2. New or worsening respiratory symptoms such as cough, dyspnea, or stridor.
3. New or worsening abdominal pain, discomfort, and/or distension with or without palpable mass including hepatosplenomegaly
4. Resolution of clinical or radiological findings of the suspected IRIS episode without change in ART, TB treatment, or additional antimicrobial therapy

Supportive observations

1. Conversion of TST negative to positive in patients receiving TB treatment and ART at time of an IRIS event, or >5x increase from baseline in interferon release assay (e.g. QuantiFERON, ELISPOT). Opinion.
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Table 4

Treatment Strategies for IRIS

Clinical Severity	Treatment Options
Mild	Observation
Moderate	NSAIDS
Severe	Corticosteroids Temporary Cessation of ART Surgical debulking
Potential Alternative Strategies	Chloroquine (anti-TNF α) Thalidomide (anti-TNF α) Leflunomide (anti-NF κ B)

No treatment has been prospectively studied in IRIS patients