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Tuberculosis Immune Reconstitution Inflammatory Syndrome in Children Initiating Antiretroviral Therapy for HIV Infection:

A Systematic Literature Review

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Abstract

Background—People with HIV initiating combination antiretroviral therapy are at risk for tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS). While this syndrome has been well researched in adults, little is known about the incidence, case fatality, underlying immunopathology and treatment approaches in children.

Methods—Major databases were searched for articles related to TB-IRIS in children. Data were abstracted using standardized forms.

Results—Thirteen studies were identified: 6 retrospective and 2 prospective cohort studies, 1 cross-sectional study, 3 case reports and 1 case series. In total, 303 cases of TB-IRIS were described, of which 270 were unmasking TB-IRIS, 12 paradoxical TB-IRIS and 21 were not classifiable due to lack of key information. None of the cohort studies had investigation of TB-IRIS as its primary aim. Nine studies were from Africa, 3 from Asia and 1 from Latin America. Age at cART initiation (reported by 12 studies) ranged from 1 month to 16 years. Median time from start of cART to IRIS diagnosis (reported by 8 studies) ranged from 8 days to 16 weeks. Few deaths attributable to TB-IRIS were recorded. Treatment was only discussed in 2 case studies, both of which reported children receiving corticosteroids. No studies evaluated risk factors for, or immunopathogenesis of, pediatric TB-IRIS.

Conclusions—There is a paucity of information available on TB-IRIS in children. Future research assessing incidence, risk factors, case fatality and optimal treatment or prevention strategies of TB-IRIS is needed.

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Keywords

tuberculosis; immune reconstitution inflammatory syndrome; pediatric HIV/AIDS; antiretroviral treatment

Despite major advances in the prevention of mother-to-child transmission of HIV, 330,000 children were newly infected with HIV in 2011. Of the estimated 3.3 million children living with HIV, the majority are in Africa and approximately 562,000 received combination antiretroviral treatment (cART) in 2011.[1-3]

cART substantially reduces the occurrence of tuberculosis (TB) and mortality in children living with HIV.[4-6] The beneficial effects are mediated by suppression of HIV replication and increased CD4 cell count.[7] In some, initiation of cART is complicated by immune reconstitution inflammatory syndrome (IRIS), whereby the individual experiences clinical deterioration within the first 6 months of initiating cART despite exhibiting immune reconstitution as evidenced by an increase in their CD4 counts and reduction in HIV-1 viral load (VL).[8] While the immunopathological processes underlying IRIS are not yet fully understood, it is generally accepted that IRIS is a consequence of an exaggerated or dysregulated immune response against a pathogen.[9] In the case of "paradoxical" IRIS, this pathogen is responsible for an infection that is diagnosed and treated; in "unmasking" IRIS, the pathogen is the cause of a latent or subclinical infection. IRIS has been associated with a wide array of pathogens, of which *Mycobacterium tuberculosis, Cryptococcus* and cytomegalovirus are the most common.[10-13]

In adults initiating cART, a meta-analysis estimated that 15.7% (95% confidence interval: 9.7–24.5%) of patients worldwide develop paradoxical TB-IRIS.[14] In addition, an estimated 5% develop unmasking TB-IRIS.[15,16] The adult case-fatality rate of TB-IRIS is relatively low, about 3.2%, with the highest case-fatality rate observed in TB-IRIS that involves the central nervous system.[14,17,18] Development of TB-IRIS in adults is known to be associated with low CD4 cell counts, disseminated TB infection and early antiretroviral therapy (ART) initiation after anti-TB treatment.[8,16,17,19] Treatment of TB-IRIS in adults generally consists of continuation of cART and continuation or initiation of appropriate anti-TB treatment, administration of non-steroid, anti-inflammatory drugs or treatment with steroids in more severe cases and interruption of cART in life-threatening cases.[20]

While many studies have investigated TB-IRIS in adults, there is a paucity of information on TB-IRIS in children. We aimed to systematically review studies that have evaluated TB-IRIS in children to define the incidence, case fatality, risk factors and treatment regimens for pediatric TB-IRIS.

MATERIALS AND METHODS

We conducted a systematic literature review on pediatric TB-IRIS. We searched the electronic databases MEDLINE and EMBASE from 1999 (when cART was introduced) to May 2013 for published reports with the terms "TB-IRIS," "HIV and IRIS," "unmasking TB," "paradoxical TB" and "TB and antiretrovirals," as well as all MeSH terms and

abbreviations relating to these terms. No language restrictions were used. Included in the review were epidemiological studies, case studies and case series, in children (0–17 years of age) receiving cART for HIV infection. Articles presenting both adult and pediatric data stratified by age were included. Similarly, articles reporting on multiple pathogen-specific types of IRIS were included if results included TB-specific IRIS. Articles were excluded if results did not distinguish between children and adults or between TB-IRIS and other types of IRIS.

Abstracts identified in the original search were independently screened by 2 reviewers (R.L.G. and A.V.R.) for inclusion and exclusion criteria. When abstracts did not include sufficient information to determine whether the article met the inclusion criteria, the article was reviewed in full. All selected articles were assessed to determine whether they met the inclusion criteria for final review. References of all selected articles were reviewed to identify potential additional eligible publications. Next, a structured data abstraction tool was used to extract study characteristics, including study design, population, location, study population demographics, baseline CD4 count or CD4 percent, baseline viral load, cART regimen, TB-IRIS definition and diagnostic criteria used by the original study, type of TB-IRIS and TB-IRIS incidence, treatment and outcomes.

RESULTS

The search yielded 385 articles, of which 320 were excluded based on abstract review (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/B745). Of the 65 full articles screened, 49 were excluded, mostly because the article did not include children, did not stratify results by children versus adults or addressed TB in people receiving cART but did not present data specifically on TB-IRIS. One additional publication was identified from the references of the 16 selected articles. Upon detailed review, 3 of these 17 articles were excluded, 1 because of insufficient information on timing of TB diagnosis in relation to starting cART, resulting in the inability to classify TB on cART as TB-IRIS, 1 due to the absence of information to reliably diagnose IRIS and 1 because of a lack of information on TB-IRIS in children.[21-23] Finally, 1 publication was excluded as it was a review of case studies already included in the articles selected for systematic review.[24,25] The remaining 13 articles included 6 retrospective cohort studies, 2 prospective cohort studies, 1 cross-sectional study, 3 case studies (1 unmasking TB-IRIS and 2 paradoxical TB-IRIS) and 1 case series reporting on 7 cases of paradoxical and 4 cases of unmasking TB-IRIS (Table 1).[25-37] In total, 303 cases of TB-IRIS were reported. Most (270, 89.1%) were cases of unmasking TB-IRIS and only 12 (4.0%) were cases of paradoxical TB-IRIS. The remaining 21 cases were not classified as paradoxical or unmasking in the original publication. Most studies did not report the extent to which TB was excluded at time of cART initiation, the age at TB-IRIS diagnosis or the median time from cART initiation to TB-IRIS diagnosis. Of the 12 publications reporting age at TB-IRIS diagnosis, the range was 1 month to 16 years. This needs to be interpreted in light of eligibility criteria for the individual studies as several studies restricted age of study participants to, for example, children <24 months or <13 years.[27,28] Among the 8 publications that reported median time from cART initiation to TB-IRIS, the range was broad, from a median of 8 days to 16 weeks.[27,33]

Only 2 articles reported on potential risk factors for TB-IRIS. Factors assessed included HIV clinical stage, baseline CD4 count or HIV viral load at cART initiation. In Shah,[32] 3 of the 7 children diagnosed with IRIS were classified as World Health Organization clinical stage 4, compared with 53% of the 30 children who remained free of IRIS during follow up. Unfortunately, results were not stratified by type of IRIS in this study, which included different types of IRIS and only 2 children with a specific diagnosis of TB-IRIS.[32] Walters et al[28] did focus specifically on the clinical presentation and outcome of TB in HIV-infected children on cART. They recorded 137 TB episodes among 290 children; 116 episodes before and 21 after cART initiation. Of these, 10 were considered probable TB-IRIS cases. Potential risk factors, such as level of immunodeficiency, World Health Organization clinical stage, nutritional status and history of TB, were compared and found to be significantly different, for children diagnosed with TB in the first 6 months of cART (n = 14) and those diagnosed with TB after 6 months of cART (n = 7). However, these risk factors were not compared between children with and without probable TB-IRIS.[28]

None of the cohort or cross-sectional studies reported on specific treatment for TB-IRIS. Two case studies recorded some treatment information. Narendran et al[36] reported successful TB-IRIS treatment in a case of paradoxical lymph nodal TB with prednisolone and continued anti-TB treatment. The child reported on by Rabie et al[37] had complications after initial anti-TB therapy and required a more complicated treatment course, consisting of oral and intravenous steroids, an intercostal drain and finally subcutaneous octreotide. Treatment appeared successful, but the child remained hospitalized for 113 days.

Few deaths were reported in children with TB-IRIS. In a study of IRIS in South African children initiating cART, 1 of 12 children diagnosed with TB-IRIS died. This child was 8 months of age and on cART for 13 days at the time of IRIS diagnosis, but also had a diagnosis of disseminated Bacillus Calmette-Guérin (BCG) disease.[27] Walters et al[28] reported 16 deaths, 15 (94%) of which occurred in children diagnosed with TB before cART initiation. According to the authors, 4 deaths may have been partly attributable to IRIS, but it was impossible to establish with certainty whether IRIS was a contributory cause of death in these children. Two cases, 1 with intestinal perforation and 1 with acute upper airway obstruction, showed good immune recovery at death but occurred >5 months after cART initiation. Two other deaths also demonstrated excellent immune recovery on cART, but both had multidrug-resistant TB.[28]

DISCUSSION

In contrast to adult TB-IRIS, very little information is available on TB-IRIS in children. Even though our analysis was based on a comprehensive search of published reports, only 13 publications could be included, of which only 3 were prospective cohort studies. None of the cohort studies identified were designed to study TB-IRIS in children. Rather, they included numerous types of IRIS or focused on any TB occurring in children on cART and were thus not limited to TB-IRIS. Consequently, the available literature did not allow us to estimate the overall TB-IRIS incidence in children initiating cART, nor the incidence of unmasking or paradoxical TB-IRIS in children. In addition, the dearth of information precluded our ability to gain any insight into risk factors for developing TB-IRIS, the case-

fatality rate of pediatric TB-IRIS or best practices for treatment of children initiating cART who develop TB-IRIS. Because of the paucity of data available, we were also not able to conduct a meta-analysis to estimate incidence, case-fatality rate or TB-IRIS risk factors.

While it is possible that pediatric TB-IRIS shares many characteristics in incidence, risk factors and immunopathogenesis of TB-IRIS in adults, the developing pediatric immune system is likely to result in important differences in host immune response and pathophysiology of TB between adults and children. Independent of coinfection with opportunistic infections, following HIV infection, children exhibit a rapid progression to disease with high early morbidity and mortality compared with adults.[38] Mechanisms likely involve a complex interplay between severely reduced HIV-specific CD4 and CD8 T cell responses and anti-HIV humoral immune responses.[39-41] For TB, both innate and adaptive immune cells form the defense against mycobacteria, but both systems can be impaired in children.[42] For example, neutrophils play an important role in the innate immune response, but infant neutrophils have decreased granulocyte functions and decreased responsiveness to cytokine stimulations.[43] Compared with adults, infant macrophages infected by *M. tuberculosis* have poorer phagocytosis.[44] Neonates also have fewer circulating dendritic cells with lower capacity to synthesize IL-12 and an impaired major histocompatibility complex II pathway, which is important for stimulation of CD8 T-cells.[29,45,46] Similar to adults, CD4 and CD8 T-cell-mediated immunity play a key adaptive role in host defense against mycobacteria, but this defense is impaired in HIV-infected children.[45,46]

To better understand the characteristics specific to pediatric TB-IRIS, additional research is needed. Prospective studies should be designed to determine the incidence and case-fatality rate of TB-IRIS in general, and paradoxical and unmasking TB-IRIS in a specific cohort of children initiating cART. Prospective studies should also evaluate whether the case definitions that have been developed for TB-IRIS in resource-limited settings are valid for the diagnosis of TB-IRIS in children in similar settings.[47] To ensure that health care workers can identify those children at highest risk of developing TB-IRIS, prospective studies should elucidate the strength of association between risk factors such as time since cART initiation, baseline viral load and baseline CD4 percentage and nutritional status and the development of TB-IRIS in children. Finally, further research is needed to understand the immunopathogenesis of TB-IRIS in children, to investigate potential overlap with BCG-IRIS and to identify the optimal treatment or prevention strategies.[48] These areas of research are particularly important given the increasing numbers of children initiating cART, especially young children, and the need for pediatric-specific cART and TB treatment regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of Retrospective Cohorts, Prospective Cohorts and Cross-sectional Studies of Pediatric TB-IRIS

Study	Publication Year	Location	Study Design	Inclusion Criteria	Definition of IRIS'	% Male	Age at ART Initiation	Any TB-IRIS*	Unmasking TB-IRIS*	Paradoxical TB-IRIS	Age at TB-IRIS*	Median Time ART Initiation to IRIS
Puthanakit et al[33]	2006	Northern Thailand	PC	<16 years, initial CD4% ≤15%, ART-naïve, no active opportunistic infection	French et al[49]	50	8 years (SD 3)	3 (2)	NR	NR	7 years (SD 5)	16 weeks
Walters et al[28]†	2008	Cape Town, South Africa	RC	HIV+ children <13 years who initiated HAART	New mycobacterial disease and/or worsening of pre-cART symptoms/ signs within 6 months of cART, immunological recovery and viral suppression	49	24 months (range 1–160)	NR	115 (40)	NR	17 months (range 2–135)	NR
Yu et al[30]	2008	Northern Malawi	RC	All patients registered for ART	NR	NR	NR	2 (1)	NR	NR	NR	87 days (range 86–87)
Wang et al[29]	2009	Lima, Peru	RC	Initiating cART and maintaining treatment for >1 years, available baseline CD4 and HIV VL	International Network of the Study of HIV-associated IRIS[50]	53	6 years (range 4 months to 16 years)	5 (6)	4 (4)	1 (1%)	6 years	NR
Smith et al[27]	2009	Johannesburg, South Africa	RC	HAART-naïve HIV+ infants <24 months who were exposed to nevirapine	French et al[49]‡	51	8 months (range 2–24 months)§	12 (7)	NR	NR	8 months (IQR: 6–11)	14 days (IQR: 13–30)
Orikiiriza et al[34]	2010	Uganda	CS	Children receiving ART 2–24 weeks	French et al[49]‡	43	6 years (IQR: 2.5–11 years)	22 (14)	11 (7)	11 (7%)	NR	NR
Bakeera-Kitaka et al[26]†	2011	Kampala, Uganda	RC	All children on ART and anti-TB treatment at a single clinic	NR	50	6 years (SD 5)		140 (8)	NR	NR	Moderate immune suppression: 15 weeks (IQR: 8–34) † Severe immune suppression: 1 weeks (IQR: 6–20) †
Okechukwu and Okechukwu[31]	2011	Abuja, Nigeria	RC	HIV+ children seen in a pediatric outpatient clinic	NR	46¶	6 years (SD 2)¶	2 (1)	NR	NR	NR	NR
Shah[32]	2011	Mumbai, India	PC	HIV+ children starting ART	Robertson et al[51]‖	54	6 years (SD 4)	2 (5)	NR	NR	NR	NR

*New or worsening clinical/radiological signs, exclusion of treatment failure or adverse drug reaction, appearance < 3 m of start cART, increase in CD4 count/CD4%.

†TB diagnosed > 3 months post-ART initiation is unlikely to be IRIS (47). Studies did not provide information on timing of individual cases.

‡≥ 1 major clinical criterion and decrease of VL ≥1 $\log_{10}$ or ≥1 major and ≥2 minor criteria.

[§] Inclusion criteria < 24 months of age.

[¶] Baseline information missing for 169 children with TB.

NR, not reported; IQR, interquartile range; SD, standard deviation; RC, retrospective cohorts; PC, prospective cohorts; CS, cross-sectional.

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TABLE 2

Characteristics of Case Studies and Case Series of Pediatric TB-IRIS

Study	Publication Year	Location	Number of Cases Described	Formally Diagnosed With IRIS?	Time From ART Initiation to IRIS	Age at ART Initiation	ART Regimen	Type of IRIS	Prior History of TB	Recent TB Contact	Basis of TB Diagnosis
Hayes et al[35]	2009	Malawi	1	No	6 weeks	17 months	NR	Unmasking	No	Yes	Mantoux test—induration of 10 mm
Narendran et al[36]	2006	India	1	Yes	8 days	12 years	Efavirenz; stavudine; lamivudine	Paradoxical	No	NR	Positive AFB sputum smear
Rabie et al[37]	2010	Cape Town, South Africa	1	Yes	11 days	3 years	Efavirenz; stavudine; lamivudine	Paradoxical	Yes	NR	Isolation from bone marrow and blood
Zampoli et al[25]	2007	Cape Town, South Africa	7	Yes	Median 25 days (IQR: 8–54)	Median 116 months (IQR: 41–121)	NR	Unmasking	Yes (3); no (4)	Yes (2); no (5)	TST (1); AFB microscopy (4); culture (4)
Zampoli et al[25]	2007	Cape Town, South Africa	4	Yes	Median 14 days (IQR: 7–63)	Median 25 months (IQR: 12–62)	NR	Paradoxical	Yes	NR	Positive AFB microscopy (3); culture (2); NR (1)

NR, not reported; AFB, acid-fast bacilli; IQR, interquartile range; TST, tuberculin skin test.