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Diagnosis and Treatment of Tuberculosis among Children at an HIV Care Program in Dar es Salaam, Tanzania

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Abstract

Diagnosis and treatment of tuberculosis is challenging in children with HIV infection. We describe the clinical features, diagnostic testing results, tuberculosis and HIV treatment, and clinical outcomes of 57 HIV-infected children diagnosed with tuberculosis at the DarDar Pediatric Program in Dar es Salaam, Tanzania. In this cohort, tuberculosis was common, microbiologic studies were frequently negative and mortality was high.

Keywords

tuberculosis; HIV infection; pediatric; children; Tanzania

Patients infected with human immunodeficiency virus (HIV) have an increased risk of disease due to *Mycobacterium tuberculosis* [1]. Consequently, tuberculosis (TB) is a leading cause of morbidity and mortality in HIV-infected patients, including children [2]. Once infected, children are substantially more likely than adults to progress to TB disease [3]. Known risk factors for HIV-TB co-disease and poor outcomes in children include low CD4 count, World Health Organization Stage 4 disease, and both acute and chronic malnutrition [4].

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The incidence of TB in children remains underreported due to difficulty obtaining sputum specimens and consequent low yield of an acid-fast bacilli sputum smear and mycobacterial culture [5]. In 2012, there were 5,280 new cases of TB in children under the age of 15 in Tanzania [6]. The Tanzanian National Tuberculosis and Leprosy Programme (NTLP) manages both pediatric and adult TB treatment in TB clinics under the Ministry of Health. Children diagnosed with TB are tested for HIV and, if positive, are referred to an HIV Care and Treatment Center. We reviewed the experience with treatment for TB among children at a pediatric HIV Care and Treatment Center in Tanzania. We sought to identify patterns in diagnosis and treatment and to assess risk factors for adverse outcomes.

MATERIALS AND METHODS

This study was performed at the DarDar Pediatric Program (DPP), a pediatric HIV clinic in Dar es Salaam, Tanzania jointly administered by the National AIDS Control Programme, Management and Development for Health, Muhimbili University of Health and Allied Sciences and the Geisel School of Medicine at Dartmouth. DPP provides HIV testing to mothers and children, enrolls those infected into care and treatment, and accepts referrals of children with TB and HIV co-disease.

We performed a retrospective review of paper and electronic records of TB diagnosis and treatment data for children enrolled at DPP between May 2006 and March 2010. Suspected TB cases were defined as children with symptoms compatible with TB disease (>2 weeks of cough and/or fever), and/or an abnormal chest radiograph suggestive of TB, and/or a history of TB exposure. Sputum samples were collected when possible. TB cases were defined as children who were started on TB treatment or who had positive mycobacterial sputum cultures and died before treatment could be initiated.

We recorded the most proximate CD4 determinations before and after TB treatment along with data on antiretroviral therapy (ART). Mortality and loss to follow up outcomes were collected at 3, 6, and 12 months after TB diagnosis.

Data were entered into Microsoft Excel (version 12.3.0, Microsoft Corporation). Comparisons between groups were conducted using Fisher's exact test for significance for categorical variables and two-sample t-tests for continuous variables.

RESULTS

As of March 2010, DPP had enrolled 1,193 children in HIV care and treatment (median age 7.6 years [range 0 – 17 years], and median CD4 count and CD4% of 587 cells/mm^3 [IQR of 307-981 cells/mm^3] and 23% [IQR of 16-31%] respectively). Among 123 (10%) children with suspected TB, there were 57 (46%) cases of TB. Of these, 43 (75%) children were referred from the NTLP with a new diagnosis of TB and HIV.

Chest radiographs were obtained on 43 of 57 children (75%), sputum smears for acid-fast bacilli in 43 (75%), mycobacterial sputum cultures in 30 (53%), and tuberculin skin tests in 34 (60%). Baseline characteristics and diagnostic testing of children at the time of TB diagnosis are shown in the Table.

Among 57 TB cases, 12 (21%) children were on ART before their TB treatment, 42 (74%) were started on ART after initiation of TB treatment, and 3 (5%) died before TB had been confirmed and before beginning ART. Of the 35 children with documented dates, the median interval from TB diagnosis to ART initiation was 70 days, with an IQR of 22-165 days. The median CD4 count and CD4% were 633 cells/mm^3 and 22% respectively at the completion of TB treatment. Among 31 children with CD4 counts pre- and post-treatment, the median CD4 increase was 301 cells/mm^3. Among the 19 children with CD4% data pre- and post-treatment, the median increase was 6%.

Treatment outcomes at 12 months from time of TB diagnosis were as follows: 45 (79%) completed TB treatment and were considered cured, 1 (2%) transferred care, 4 (7%) were lost to follow-up, and 7 (12%) died. Four of the 7 deaths (7%) occurred within 2 months of TB diagnosis and the remaining 3 deaths (4%) occurred between 2 and 6 months after diagnosis. Among children who died within 6 months, 4 of 7 (57%) were on ART at the time of death, and 3 of 4 (75%) had been on ART for at least one month at the time of death. Fatal cases were more likely to have positive mycobacterial cultures (Table). Among 45 children with follow up information three years after treatment, 36 children (80%) were alive, and 9 (20%) had died;, there were no reported TB treatment failures.

DISCUSSION

We found that treatment for TB was common and attendant mortality high among a cohort of HIV-infected children in Dar es Salaam, Tanzania. The rate of TB in our cohort was slightly lower than another study reported recently from Dar es Salaam [4]. As has been observed repeatedly, most children had negative microbiologic studies, negative tuberculin skin tests and were treated based on clinical findings [1]. TB cases had low absolute CD4 counts and CD4%s. The majority had been diagnosed with TB at the NTLP program, where they were found to also be infected with HIV, and subsequently referred for initiation of ART. Thus, the TB diagnosis preceded the HIV diagnosis, a sequence that could be reversed by wider screening of at-risk pregnant women and children for HIV and thorough evaluation of contacts of infectious TB cases.

Children with fatal outcomes tended to have lower CD4 counts, and a higher frequency of positive microbiology. Five of the 9 deaths (56%) occurred within 3 months of the TB diagnosis and only 2 of these 5 had been started on ART. These data emphasize the importance of screening for TB in all children with a new diagnosis of HIV, repeat evaluation if symptoms develop (especially in those with additional risk factors such as low CD4%), and the importance of early ART initiation at the time of a new TB diagnosis. Among adults with HIV, recent trials confirmed that mortality is reduced when ART is started within 8 weeks of TB treatment and within 2 to 4 weeks for those with CD4 counts <50 [7]. These new data resulted in revised recommendations for initiating ART within 2 weeks of starting TB treatment [8]. ART treatment was shown to significantly improve CD4 count and CD4% in the 31 children with follow-up CD4 data. Since most (42 of 57) children started ART while on TB treatment, improvements in CD4 count and CD4% at the completion of TB treatment likely reflect the effect of initiating both therapies.

Our findings support the need for continued focus on improved prevention of TB infection and disease in children. Early diagnosis and ART treatment are essential. In a study of children predominantly older than 2 years of age and with low rates of prior ART, the use of isoniazid preventive therapy reduced both TB disease and overall mortality [9]. BCG is contraindicated in children with known HIV infection, but should be administered routinely to all children at birth when HIV testing is not available. An inactivated whole cell vaccine has been shown effective in preventing TB in HIV-infected adults with prior BCG, and will be evaluated as a BCG booster in adolescents [10].

Our analysis is limited primarily by its retrospective nature, small sample size and our incomplete TB treatment data available from the NTLP. In addition, data on demographic, laboratory, and treatment features of the entire HIV cohort were not available to compare to the subset of children with TB. We were unable to accurately assess the incidence of immune reconstitution inflammatory syndrome (IRIS); however, our review of the medical records, including post mortem follow up from parents/caregivers did not reveal clinical histories consistent with IRIS. Despite these limitations our review has allowed us to identify potentially remediable deficiencies in HIV and TB co-disease care and treatment in this setting.

Our findings emphasize the critical importance of early HIV diagnosis and initiation of ART at recommended CD4 thresholds for children, including at time of a new TB diagnosis. ART reduces TB risk substantially as has been shown recently among children in Tanzania [4]. Further, careful and regular surveillance for TB should include measures currently employed in our programs: symptom screening in all children, with a particular focus on children with CD4% less than 15%, children with a prior episode of TB, and children with malnutrition.

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Table 1

Characteristics of fatal and non-fatal cases of Tuberculosis

	All cases N=57	**Fatal cases[a] N=7**	**Non-fatal cases N=50**	**P value**
Median Age in years	8.1	10.2	7.5	p=.63[b]
Male Sex	34 (57%)	4 (57%)	26 (52%)	p = .80[c]
Median baseline CD4	248	62 (n=5)	262 (n=49)	p=.42[b]
Median baseline CD4 %	13%	4% (n=5)	14% (n=37)	p = .766[b]
Sputum smear positive	0/43 (0%)	0 (0%)	0 (0%)	
Sputum culture positive	6/30 (20%)	3/4 (75%)	3/26 (12%)	p=.02[c]
Tuberculin skin test positive[d]	5/34 (15%)	0/3 (0%)	5/31 (16%)	p=.49[c]
On ART at time of TB diagnosis	12 (21%)	2 (29%)	10 (20%)	p=.63[c]
Placed on ART within 8 weeks[e]	17/35 (49%)	3/5 (60%)	14/40 (35%)	p=.35[c]

ART: antiretroviral therapy

[a] Fatal cases refers to those in which the child died within 6 months of TB treatment initiation.

[b] P-values calculated using standard two sample t-test.

[c] P-values calculated Fisher's exact test.

[d] Defined as ≥5mm induration.

[e] Among 35 children with documented TB diagnosis dates and ART start dates.