Incidence and Risk Factors Associated with Tuberculosis in HIV-positive Children Receiving Antiretroviral Therapy in a Large South African Multicenter Cohort

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BACKGROUND

Tuberculosis (TB) in children and adolescents is a direct consequence of adult TB and is a good marker of current trends in community transmission.

OBJECTIVE

We sought to estimate rates of, and risk factors for, incident TB (defined as patients receiving TB treatment, including both bacteriological and clinical diagnosis) amongst HIV-infected children and adolescents (children<5 years of age and 5-18 years of age) receiving antiretroviral treatment (ART) in South Africa.

METHODS

STUDY POPULATION:

We conducted a cohort analysis of HIV-infected children ≤18 years of age who were enrolled in care between April 2004 and May 2011 at one of 12 HIV clinics in Gauteng and Mpumalanga provinces. Clinical and laboratory data were collected prospectively on TherapyEdge-HIV™ clinical decision support software, as part of routine HIV care at the clinics. National TB guidelines throughout the study period indicated that HIV-positive adolescents with symptoms suggestive of TB should have a smear and culture done to confirm diagnosis. For children the diagnosis of TB is based on a combination of history of exposure, clinical presentation, Mantoux test and chest x-ray. Children and adolescents diagnosed with TB while on ART should continue ART throughout TB treatment. HIV-infected children diagnosed with TB prior to ART initiation were eligible for ART initiation regardless of CD4 count or percentage.

STATISTICAL METHODS:

- We calculated crude rates of TB for the overall population.
- We used log-binomial regression with a Poisson distribution to determine predictors of TB risk for children <5 and for those 5-18 years, separately, controlling for, gender and current predictors of TB (e.g. age, duration on ART, viral load and hemoglobin).
- For children <5 we also controlled for CD4 percent and weight-for-age Z-score over time.
- For children 5-18 we also controlled for CD4 count and body mass index (BMI) over time.

RESULTS

Table 1. Demographic and clinical characteristics (N=3329)

Variable		Age at ART initiation: < 5 years (n=1174)	5-18 years (n=2155)	Total (n=3329)
Sex	**Female**	605 (51.5)	1116 (51.8)	1721 (51.7)
	Male	569 (48.5)	1039 (48.2)	1608 (48.3)
Weight-for-age Z-score	**Normal**	881 (75.0)	-	881 (75.0)
	Mod Severe	293 (25.0)	-	293 (75.0)
CD4 at ART initiation (cells/mm³)	**>350**	-	556 (25.8)	556 (25.8)
	200-350	-	299 (13.9)	299 (13.9)
	101-200	-	425 (19.7)	425 (19.7)
	51-100	-	359 (16.7)	359 (16.7)
	≤50	-	516 (23.9)	516 (23.9)
CD4 percentage at ART initiation	**≥25**	546 (46.5)	-	546 (46.5)
	<25	628 (53.5)	-	628 (53.5)
WHO stage at ART initiation	**I/II**	786 (67.0)	1598 (74.2)	2384 (71.6)
	III	325 (27.7)	450 (20.9)	775 (23.3)
	IV	63 (5.4)	107 (5.0)	170 (5.1)
		Median (IQR)		
Age at ART initiation (years)		1.4 (0.7-2.5)	8.3 (5.9-11.6)	5.6 (2.1-9.5)
CD4 count at ART initiating (cells/mm³)		-	264 (107.4-513)	264 (107.4-513)
Hemoglobin at ART initiation (g/dL)		9.8 (8.3-11.2)	10.6 (9.0-12.1)	10.3 (8.7-11.9)
BMI at ART initiation (kg/m²)		-	14.2 (10.9-17.2)	14.2 (10.9-17.2)

MAIN FINDINGS:

- During 2,828 person-years of follow-up, 113 TB cases (diagnosis confirmed by sputum microscopy) occurred among 3,329 pediatric ART patients.
- Overall incidence rate of 4.0 cases/100 person-years (95% CI: 3.3-4.8).
- The highest incidence rate was observed in the first 6-months on ART (5.9/100 person-years; 95% CI: 4.7-7.4).

Table 2. Incidence rates and risk factors of tuberculosis among children and adolescents (N=3329)

Variable		TB events/ person-years	Rates (per 100 person-years)	Adjusted Model <5 year olds RR (95% CI)	Adjusted Model 5-18 years RR (95% CI)
Age (years) for children <5	**1-5**	41/894.8	4.6 (3.3-6.2)	Reference	-
	<1	17/206	8.3 (4.8-13.2)	1.27 (0.65-2.49)	-
Age (years) for children ≥5	**≥10**	21/751.5	2.8 (1.7-4.3)	-	Reference
	5-9.9	34/975.8	3.5 (2.4-4.9)	-	2.43 (0.98-5.99)
Current viral load (copies/mL)	**<400**	37/1,414.8	2.6 (1.8-3.6)	Reference	Reference
	≥400	76/1,413.3	5.4 (4.2-6.7)	1.68 (0.77-3.67)	1.16 (0.50-2.68)
Current CD4 Count (cells/mm³)	**<100**	11/147.8	7.4 (3.7-13.3)	-	4.60 (1.49-14.2)
	100-199	11/156.3	7.0 (3.5-12.6)	-	3.22 (1.28-8.05)
	200-349	10/265.3	3.8 (1.8-6.9)	-	2.37 (0.91-6.15)
	350-499	6/267	2.2 (0.8-4.9)	-	1.49 (0.34-6.56)
	≥500	17/891	1.9 (1.1-3.1)	-	Reference
Current CD4 Percent	**≥25**	28/580	4.8 (3.2-7.0)	Reference	-
	<25	30/520.8	5.7 (3.9-8.2)	1.14 (0.57-2.26)	-
Time on ART (months)	**≥6**	30/1,431.8	2.1 (1.4-3.0)	Reference	Reference
	<6	83/1,396.3	5.9 (4.7-7.4)	2.16 (1.12-4.16)	2.07 (1.15-3.74)
Gender	**Female**	56/1,447.3	3.9 (2.9-5.0)	Reference	Reference
	Male	57/1,380.8	4.1 (3.1-5.3)	1.12 (0.65-1.95)	0.93 (0.54-1.61)
Current Body Mass Index (kg/m²)	**≥18.5**	11/490.3	2.2 (1.1-4.0)	-	Reference
	<18.5	44/1237	3.6 (2.6-4.8)	-	1.42 (0.50-4.03)
Current Weight-for-age Z-score	**Normal**	41/881.25	4.7 (3.3-6.3)	Reference	-
	Mod/Sev	17/219.5	7.7 (4.5-12.4)	1.17 (0.5-2.68)	-
Current Hemoglobin (g/dL)	**≥10.0**	74/2,323	3.2 (2.5-4.0)	Reference	Reference
	<10.0	39/505	7.7 (5.5-10.6)	1.74 (0.63-4.84)	1.71 (0.81-3.60)

MAIN FINDINGS (Cont.):

- Log-binomial models for children <5 years and 5-18 years showed all patients had over a 2-fold increase in the risk of TB in the first 6-months on ART compared to >6-months (Table).
- In children <5 years of age:
  - those with a detectable viral load (>400 copies/mL) had a 70% increase in the risk of TB compared to those children who achieved viral load suppression (risk ratio (RR): 1.7; 95% CI: 0.8-3.7)
  - patients with a low hemoglobin (<10 ug/dL) (<5 years - risk ratio (RR): 1.7; 95% CI: 0.6-4.8 and 5-18 years - RR 1.7; 95% CI: 0.8-3.6) were also at increased risk
- In children 5-18 years of age:
  - those younger in age (5-9.9 vs. >10 years-RR 2.4; 95% CI: 1.0-6.0) were at increased risk of TB
  - patients with low current CD4 count (<200 vs. >500 – RR 4.6; 95% CI: 1.5-14.2) were at increased risk of TB

LIMITATIONS

Our results should be considered alongside the limitations of this observational cohort study. First, TB diagnosis in children is difficult to confirm, as it is usually paucibacilliary and small children are unable to produce sputum. During the long period of the study, there was a growing awareness of TB disease in children and it is possible that the difficulties of diagnosis led to both under and over diagnosis over time and in different settings. Approximately 45% of TB diagnoses in children included in our analysis were based on clinical symptoms and did not have laboratory confirmation. Second, according to South African national guidelines, children who are HIV infected should be on isonaizid prophylaxis (IPT); however, we were unable to control for the use or non-use of IPT in our analysis. Finally, since 2004 HIV-infected children with TB have been eligible for ART initiation regardless of CD4 values; thus, the rates of incident TB after initiation on ART cannot be directly compared to similar rates in adults who had to be both TB/HIV co-infected and have a CD4<200 to initiate.

CONCLUSIONS

Our results show that younger age and poor immunologic response to treatment are associated with increased risk of TB. Patients are also at increased risk of TB in the first 6-months after initiation onto ART, potentially a result of immune reconstitution inflammatory syndrome (IRIS). Early ART initiation and intensified TB screening at ART initiation may help improve treatment outcomes in younger HIV-positive children and adolescents.

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