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Tuberculosis along the continuum of HIV care in a cohort of adolescents living with HIV in Ethiopia

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Summary

Setting: Eight health facilities in two regions of Ethiopia

Objective: To determine TB incidence rates and associated factors among adolescents living with HIV in Ethiopia.

Design: This was a retrospective cohort study. Adolescents enrolled in HIV care between January 2005-December 31 2013 constituted the study population. The main outcome variable was diagnosis of TB during follow up. Baseline WHO clinical stage, CD4 count, previous history of TB and the use of isoniazid preventive therapy (IPT) were main independent variables. We estimated TB incidence rates as incident cases per 100 person-years of observation (PYO). The Cox regression analysis was used to control for confounders.

Results: Of 1072 adolescents studied, 60.1% were girls. TB incidence rate was 16.32 per 100 PYO during pre-antiretroviral therapy (pre-ART) follow up but declined to 2.25 per 100 PY after initiation of ART. Advanced WHO clinical stage (adjusted Hazard Ratio, aHR=2.71; 95% CI=1.69, 4.33) and CD4 count <350 cells/ml [(aHR=2.28 (1.10, 4.81)] predicted TB incidence in the pre-ART cohort. IPT use was associated with significant reduction in TB incidence in the ART cohort.

Conclusion: TB was a significant problem in adolescents living with HIV but it can be reduced significantly if ART and IPT are administered adequately.

INTRODUCTION

Tuberculosis (TB) is a global public health problem, with about 9 million new infections and 1.5 deaths occurring in a year.[1] People living with HIV (PLHIV) comprised 13% of all TB deaths. However, there is limited data on the contribution of TB in adolescents to the global TB burden. In fact, lack of adolescent-specific health data is a global challenge. [2] Older epidemiologic data suggest increased incidence of TB during adolescence [3, 4], and the risk of TB infection is highest during infancy and adolescence.[5-7]More recent data suggested high prevalence of TB among adolescents aged 12-18 years.[8]

Since adolescents are socially active, their potential to transmit to their peers is high and risk factors such as smoking, substance use, and stress are more common among adolescents increasing their likelihood of developing TB and eventually transmitting to their peers. [9-11] Also, with more and more perinatally HIV infected children growing to adolescence, it is important to have clearer understanding of both the magnitude and factors contributing to TB incidence in this age group in order to plan for appropriate preventive measures.[10,11]

Data on the magnitude and determinants of TB among adolescents are scarce and when reported, they are not generally focused on HIV infected adolescents or separately report on the age group 10-19 years of age. [8, 12-14]Our objective was to determine the magnitude of TB among adolescents at each phase of HIV care cascade in a cohort of ALHIV treated and followed at selected public health facilities in Ethiopia. [15]

METHODS

Study setting

This study was conducted in eight health facilities in Addis Ababa and Southern Nations', Nationalities' and Peoples' Regional State (SNNPR) regions of Ethiopia. Addis Ababa is the capital city of Ethiopia whereas SNNPR is a predominantly rural region, although most of HIV patients are concentrated in urban areas even in SNNPR. The eight health facilities were selected based on the high load of ALHIV, according to the investigators' prior knowledge about the sites. Despite the good progress made in preventing and controlling HIV and TB, Ethiopia belongs to high HIV and TB burden countries.[16, 1]

Study design

We used a retrospective cohort study design. The study population constituted adolescents (age 10-19 years inclusive) enrolled in chronic HIV care between January 2005-December 31 2013. Participants had to have at least one documented clinic visit and be ART-naïve at the time of enrolment in chronic HIV care in the study clinic.

Per the national guidelines, all PLHIV were screened for symptoms of TB at baseline and then at each clinic visit. Symptomatic patients received further clinical evaluation and diagnostic tests. The first line diagnostic test during the cohort period was conventional sputum microscopy. Chest radiography was done on selected cases upon physicians' recommendation. Rapid TB diagnostic tests were not part of the national guidelines at the time this cohort was enrolled. [17]

To calculate the sample size, we used the baseline WHO clinical stage as main predictor of TB and those in stage III-IV were considered "exposed" groups. Assuming a two-sided alpha of 0.05, power of 0.8, TB in the exposed group as 10%, and TB in the unexposed group as 5%, we calculated minimum sample size of 948. The assumptions were based on preliminary analyses of data from ongoing larger cohort study in the study site. Using an electronic access database maintained at each ART clinic, we generated age-stratified list of patients as a sampling frame. Since the number of eligible adolescents was close to the estimated sample size, we included all eligible adolescents in the study.

Data collection and management

We used patient charts and registers as data sources. At each site, two study nurses assisted by data clerks retrieved information using a data abstraction form. At the end of each work week, the site study nurses submitted all completed data abstraction forms to the co-

investigator in the respective region. The co-investigator, who is a pediatrician with specialist level training in HIV, checked for errors and omissions and forwarded the paper data forms to the centrally based research assistant for further quality check and for secure storage. A centrally based data clerk entered data from checked and approved data abstraction forms into SPSS version 22.0. Electronic data were stored in a password protected data storage device and the paper data forms were kept in a lockable shelf. No patient identifiers were included in the electronic data.

The data abstraction tool was piloted in a few sites before starting actual data abstraction. All staff involved in data management were trained on the standard operating procedures of the study protocol. The principal author did random checks of the completed data abstraction forms at regular intervals.

Definitions

The main outcome variable was diagnosis of TB during follow up as confirmed and recorded in patient registers according to the national guidelines by the treating clinician. [24] Patients in whom TB diagnosis was confirmed at least four weeks after the patient was in pre-ART care but before the ART start date were defined to have **pre-ART TB**. Patients who developed TB after four weeks of ART initiation were considered to have **TB during ART**.

We determined **IPT completion rates** from patient registers. Those who completed a 6-month course of IPT and labelled by the clinicians as such were considered "completed"; those who received for less than 6 months were categorized as "did not complete"; and those with missing information were categorized as "no information".

Information on **adherence to co-trimoxazole therapy (CPT)** was also retrieved from patient registers. Clinicians recorded either "good" or "poor" based on patients' self-report. We determined the adherence status as per the clinician's record during the patients' last visit.

Data analysis

We used SPSS version 22 for data analysis. We calculated TB incidence rate as number of new episodes of TB per 100-person years of observation. We checked for patterns of missing data and used list-wise deletion method for missing variables. A cox regression survival analysis was used to control for potential confounders. TB diagnosis (as defined above) was the main outcome variable. We included baseline WHO clinical stage, CD4 count (categorized as <350 versus >=350 cells/ml for the pre-ART cohort and <200 versus >=200 cells/ml for the ART

cohort), history of cough of more than 2 weeks, and IPT (ever used or not). Co-variates included sex and address (as urban or rural) in the Cox model. Co-variates which had a p-value of <0.25 in the univariate model were included in to the multivariate model. Two-sided $p<0.05$ was considered statistically significant.

Ethics

National, Regional and Institutional Review committees approved the protocol. All research staff were trained on the ethical conduct of Human Subjects Research. Measures to protect data security and confidentiality are described above.

RESULTS

Baseline characteristics

Of 1,221 adolescents screened, 1,072 fulfilled the eligibility criteria and were included in the analysis; 60.1% were girls and 87% came from urban areas. Half (50.7%) presented at an advanced WHO stage. Baseline CD4 values were available for 95.3% of patients and their median CD4 count per ml was 228. Table 1 describes baseline characteristics of the participants. Only 142 (13.2%) of the patients received IPT during the entire follow up (57 during pre-ART follow up and 85 at, or after ART initiation). Of these, 103 (72.5 %) completed full course of IPT, 22 (15.5%) did not complete, and information was missing in 17 (12%). On the other hand, 84.5% of adolescents received CPT with 68.9% of them reported to have good CPT adherence rate at last visit.

TB during pre-ART follow up

Previous history of TB was present in 171 (16%) of the participants. A further 149 (13.9%) had history of TB at enrollment of which 50.3% had smear positive pulmonary TB, 28.8% smear negative pulmonary TB, 14.1% extra-pulmonary TB, and type of TB was not recorded in 6.7%. The total pre-ART follow up period was 870.03 PYO during which 142 adolescents were diagnosed with active TB. Of these, 46% had previous history of TB at baseline. The TB incidence density (95% Confidence Interval, CI) was 16.32 (13.75, 19.24) per 100 PY.

Having advanced WHO clinical stage (aHR=5.68; 95% CI=3.72-8.68), CD4 count <350 count per ml at baseline (aHR=1.85 95% CI=1.21, 2.84), previous history of TB (aHR=2.22; 95% CI=1.51-3.26), and history of cough of > 2 weeks (aHR=4.25; 95%CI=2.81-6.44) predicted TB. IPT was associated with reduction in TB incidence rate but this was not statistically significant (aHR=0.55; 95% CI=0.16-1.91). See **Table 2**.

TB after ART initiation

Of 816 put on ART, 98 were on anti-TB treatment at ART initiation including 58 in intensive and 40 in continuation phases of treatment. Further, 64 patients developed TB during 2843.53 PYO, yielding TB incidence rate of 2.25 (95% CI, 1.78-2.86) per 100 PYO after ART initiation. The incidence rate was highest during the first year of ART (16.7 per 100 PYO) compared with 2.3 and 1.6 per 100 PYO between 1-5 yr and more than 5 yr respectively. Being in advanced WHO clinical stage (aHR=1.23; 95% CI=0.63, 2.38); having CD4 count <200

cells/ml at baseline (aHR=1.92; 95% CI=1.07, 3.43); and being from SNNPR (aHR=2.69; 95% CI=1.52, 4.78) predicted higher TB rates. On the other hand, IPT use was associated with significantly lower TB incidence rate (aHR=0.06; 95%CI=0.01, 0.45). Table 3 summarizes results for the ART cohort.

DISCUSSION

This is the first report of ALHIV-specific TB data from Ethiopia and perhaps one of a few globally. We found a high TB incidence rate among ALHIV, especially during pre-ART and the first year of ART, and declined sharply after the first year of ART. Low baseline CD4 values, advanced clinical disease stage, previous history of TB, and presence of prolonged cough at baseline predicted occurrence of TB. IPT was associated with 94% reduction in TB incidence rate in the ART cohort. Our findings suggest the need to prioritize ALHIV for TB prevention and highlight the need to be watchful for specific risk factors during clinical care of adolescents.

Both the pre-ART and after ART TB rates in our cohort are at least ten times higher than those reported among non-HIV infected adolescents. In a rural Uganda, for example, the incidence of TB among adolescents aged 12-18 years was 0.235 per 100 PYO. [13] Among adolescents in a South African school, TB incidence rate was 0.45 per 100 PYO.[18]

The pre-ART TB incidence rate in our study is higher than what was reported in adult cohorts from similar settings. In two reports from southern Ethiopia, pre-ART TB incidence ranged from 9.9-11.1 per 100 PYO. [19, 20] However, the overall TB incidence rate of 2.25 per 100 PYO in adolescents who received ART in our study is lower than a rate of 3.7 per 100 PYO in an adult cohort from southern Ethiopia. [20]In Addis Ababa, TB incidence rate was 3.1 per 100 PYO in adult cohort of patients on ART. [21]In a South African adult cohort, TB incidence rate declined from 3.5 per 100 PYO in the first year to 1.01 per 100 PYO in the fifth year.[22] The heightened risk of TB among adolescents in the current study despite improved TB prevention and control efforts in Ethiopia is a clear indication to prioritize ALHIV as key populations for TB prevention.[1]

The predictive value of CD4 count and WHO clinical stage are well documented in adult cohorts. [23, 24]We found similar results in the pre-ART cohort but we did not find significant association between TB incidence and WHO clinical stage after ART. This suggests that CD4 count may be a more reliable predictor of TB incidence in the adolescent cohort compared with the WHO clinical stage.

Despite its proven effectiveness, IPT coverage was low in this age group. Our finding concurs with results from similar settings. This further confirms the need to strengthen IPT implementation. [24]

The higher TB incidence rate among ART patients from SNNPR was an unexpected finding. It could be a reflection of variations in disease burden or a result of differences in case finding efforts. Further analysis of epidemiologic data is needed to better explain the regional variations. .

Previous history of TB was associated with more than doubling in the risk of TB in this cohort. Earlier studies among adult cohorts reported conflicting results [22,] but a more recent study from Brazil reported doubling in the risk of TB in patients who had previous history of TB, and about 38% of the patients in that report had previous history of TB.[26] In our cohort, about 46% of patients who developed TB during pre-ART follow up had previous history of TB which could be due to the higher overall TB burden in Ethiopia.[1] Reinfection due to weakened immune status is the underlying reason for TB recurrence in PLHIV. [27, 28] Since our cohort includes patients from pre-ART era over a decade ago, they might have had TB and treatment for it long before starting ART. Our finding suggests the need for including previous history of TB as part of the routine screening checklists in high TB/HIV burden settings.

Our study has some limitations. TB diagnosis was made based on microscopy or radiography potentially leading to underestimation of incident TB cases because of the low sensitivity of the diagnostic method. Because of the retrospective data collection method, we were not able to determine the outcomes of treated TB cases and data were missing on some key potential predictors such as smoking. Nevertheless, to our knowledge these are the first adolescent-specific TB data among PLHIV in Ethiopia and likely will have broader implications with increasing numbers of HIV-infected adolescents globally.

CONCLUSIONS

We found a high rate of TB incidence among ALHIV in public health facilities in two regions of Ethiopia. IPT and ART had protective effect. However, the IPT coverage rate was unacceptably low in this age group. The first year of ART was the period with highest rates of incident TB cases followed by the pre-ART period. TB programs should prioritize ALHIV as priority target groups for TB prevention and control efforts, especially up to the first year after ART. Strengthening school TB programs, contact investigation among adolescents, early IPT and adequate IPT coverage should be considered urgent priorities. Prospective studies with more comprehensive variables will provide further insights about the high TB rate in this age group.

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CONFLICT OF INTEREST

None declared.

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Tables

Table 1: Baseline characteristics of adolescents enrolled in chronic HIV care at eight selected health facilities, 2005-2013, Ethiopia

Characteristic	Value
Region, N (%)	
SNNPR	582 (54.3)
Addis Ababa	490 (45.7)
Total	1072 (100%)
Median age in years	13
Sex, N (%) girls	644 (60.1)
WHO stage, N (%)	
I-II	501 (46.7)
III-IV	544 (50.7)
Missing	27 (2.5)
Total	1072 (100)
Median CD4 (IQR)	228 (106-410)

Legend
SNNPR=Southern Nations', Nationalities' and Peoples' Region

Table 2. Cox Regression Analyses of Predictors of pre-ART TB incidence in adolescents living with HIV, 2005-2013, Ethiopia

Variable	Incident TB case	Person-years	Incident rate per 100 PYO	Unadjusted HR (95% CI)	Adjusted HR (95%CI)
Region					
Addis Ababa	69	437.51	15.77 (12.27, 19.96)	Ref	Ref
SNNPR	73	432.53	16.88 (13.23, 21.22)	1.09 (0.79, 1.52)	1.14 (0.80, 1.62)
Sex					
Female	85	531.11	16.00 (12.78, 19.79)	Ref	Ref
Male	57	336.31	16.95 (12.84, 21.96)	1.02 (0.73, 1.43)	1.07 (0.75, 1.52)
Cough*					
No	49	712.90	6.87 (5.08, 9.09)	Ref	Ref
Yes	91	119.32	76.27(61.40, 93.64)	9.51 (6.72, 13.45)	1.85 (1.21, 2.84)
WHO stage*					
I-II	30	640.84	4.68 (3.22, 6.59)	Ref	Ref
III-IV	108	217.73	49.6 (40.9, 59.6)	6.78 (4.48, 10.23)	2.71 (1.69, 4.33)
CD 4 count*					
>=350	42	573.36	7.32 (5.35, 9.81)	Ref	Ref
<350	96	270.77	35.45 (28.72, 43.30)	2.81 (1.92, 4.12)	1.85 (1.21, 2.84)
Pre-ART IPT					
No	139	715.97	19.41 (16.38, 22.85)	Ref	Ref
Yes	3	154.06	1.95 (0.49, 5.30)	0.16 (0.05, 0.50)	0.57 (0.17, 1.86)
Previous history of TB					
No	76	870.04	8.73 (6.88, 10.93)	Ref	Ref
Yes	66	84.84	77.78 (60.16, 98.97)	6.23 (4.45, 8.69)	2.22 (1.51-3.26)

Legends:

*** numbers do not add up to 142 because of missing data**

SNNPR=Southern Nations', Nationalities', and Peoples' Region

HR=Hazard ratio; HR= hazard ratio; PY=person-years

Table 3. Cox Regression Analyses of Factors Associated with TB incidence rate after ART, 2005-2013, Ethiopia

Variable	Incident TB case	Person-years	Incident rate per 100 PYO	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95%CI)
Region					
Addis Ababa	40	2009.76	1.99 (1.44, 2.68)	Ref	Ref
SNNPR	24	833.77	2.88 (1.89, 4.22)	1.96 (1.16, 3.32)	2.69 (1.52, 4.78)
Sex					
Female	25	1638.70	1.53 (1.01, 2.22)	Ref	Ref
Male	39	1202.75	3.24 (2.24, 4.39)	1.01 (0.61, 1.67)	1.09 (0.65, 1.84)
Cough					
Yes	12	557.39	2.15 (1.17, 3.66)	Ref	Ref
No	52	2070.83	2.51 (1.89, 3.27)	1.09 (0.58, 2.05)	1.11 (0.55, 2.21)
WHO stage*					
I-II	12	785.00	1.53 (0.83, 2.59)	Ref	Ref
III-IV	51	2039.84	2.50 (1.88, 3.26)	1.21 (0.64, 2.31)	1.23 (0.63, 2.38)
CD 4 count					
>=200	16	1034.02	0.9(0.51, 1.46)	Ref	Ref
<200	48	1776.82	4.64 (3.42, 6.15)	1.73 (0.98, 3.05)	1.92 (1.07, 3.44)
Ever used IPT					
No	63	2387.82	2.64 (2.04, 3.35)	Ref	Ref
Yes	1	455.71	0.22 (0.01, 1.08)	0.08 (0.01, 0.57)	0.06 (0.01, 0.45)
Previous history of TB					
No	53	2202.88	2.41 (1.80, 3.15)	Ref	Ref
Yes	11	635.26	1.73 (0.86, 3.09)	0.57 (0.29, 1.10)	0.64 (0.32, 1.28)

*Numbers do not add up to 64 because of missing data