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

3

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15

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32

33 **Summary**

34 **Setting:** Eight health facilities in two regions of Ethiopia

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

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

43 **Results:** Of 1072 adolescents studied, 60.1% were girls. TB incidence rate was 16.32 per
44 100 PYO during pre-antiretroviral therapy (pre-ART) follow up but declined to 2.25 per 100 PY
45 after initiation of ART. Advanced WHO clinical stage (adjusted Hazard Ratio, aHR=2.71; 95%
46 CI=1.69, 4.33) and CD4 count <350 cells/ml [(aHR=2.28 (1.10, 4.81)] predicted TB incidence in
47 the pre-ART cohort. IPT use was associated with significant reduction in TB incidence in the
48 ART cohort.

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

51

52 INTRODUCTION

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

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

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

71

72 **METHODS**

73 **Study setting**

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

81 **Study design**

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

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

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

99 **Data collection and management**

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

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

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

114 **Definitions**

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

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

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

127 **Data analysis**

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

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

138 **Ethics**

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

142

143

144 **RESULTS**

145 **Baseline characteristics**

146 Of 1,221 adolescents screened, 1,072 fulfilled the eligibility criteria and were included in
147 the analysis; 60.1% were girls and 87% came from urban areas. Half (50.7%) presented at an
148 advanced WHO stage. Baseline CD4 values were available for 95.3% of patients and their
149 median CD4 count per ml was 228. Table 1 describes baseline characteristics of the participants.
150 Only 142 (13.2%) of the patients received IPT during the entire follow up (57 during pre-ART
151 follow up and 85 at, or after ART initiation). Of these, 103 (72.5 %) completed full course of
152 IPT, 22 (15.5%) did not complete, and information was missing in 17 (12%). On the other hand,
153 84.5% of adolescents received CPT with 68.9% of them reported to have good CPT adherence
154 rate at last visit.

155 **TB during pre-ART follow up**

156 Previous history of TB was present in 171 (16%) of the participants. A further 149
157 (13.9%) had history of TB at enrollment of which 50.3% had smear positive pulmonary TB,
158 28.8% smear negative pulmonary TB, 14.1% extra-pulmonary TB, and type of TB was not
159 recorded in 6.7%. The total pre-ART follow up period was 870.03 PYO during which 142
160 adolescents were diagnosed with active TB. Of these, 46% had previous history of TB at
161 baseline. The TB incidence density (95% Confidence Interval, CI) was 16.32 (13.75, 19.24) per
162 100 PY.

163 Having advanced WHO clinical stage (aHR=5.68; 95% CI=3.72-8.68), CD4 count <350
164 count per ml at baseline (aHR=1.85 95% CI=1.21, 2.84), previous history of TB (aHR=2.22;
165 95% CI=1.51-3.26), and history of cough of > 2 weeks (aHR=4.25; 95%CI=2.81-6.44) predicted
166 TB. IPT was associated with reduction in TB incidence rate but this was not statistically
167 significant (aHR=0.55; 95% CI=0.16-1.91). See **Table 2**.

168 **TB after ART initiation**

169 Of 816 put on ART, 98 were on anti-TB treatment at ART initiation including 58 in
170 intensive and 40 in continuation phases of treatment. Further, 64 patients developed TB during
171 2843.53 PYO, yielding TB incidence rate of 2.25 (95% CI, 1.78-2.86) per 100 PYO after ART
172 initiation. The incidence rate was highest during the first year of ART (16.7 per 100 PYO)
173 compared with 2.3 and 1.6 per 100 PYO between 1-5 yr and more than 5 yr respectively. Being
174 in advanced WHO clinical stage (aHR=1.23; 95% CI=0.63, 2.38); having CD4 count <200

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

179

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

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

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

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

231

232 **CONCLUSIONS**

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

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251 **CONFLICT OF INTEREST**

252 None declared.

253

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255

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- 330

331 **Tables**

332

333 **Table 1: Baseline characteristics of adolescents enrolled in chronic HIV care at eight selected health**
334 **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)

335

336 **Legend**

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

338
 339 **Table 2. Cox Regression Analyses of Predictors of pre-ART TB incidence in adolescents living with HIV,**
 340 **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)

341

342 **Legends:**343 *** numbers do not add up to 142 because of missing data**

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

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

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347

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353**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)

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