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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 Ethiopia.

OBJECTIVE: To determine tuberculosis (TB) incidence rates and associated factors among adolescents living with the human immunodeficiency virus (ALHIV).

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

RESULTS: Of the 1221 adolescents screened, 1072 were 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 PYO 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/μl (aHR 2.28, 95%CI 1.10–4.81) predicted TB incidence in the pre-ART cohort. IPT use was associated with a significant reduction in TB incidence in the ART cohort, but not in the pre-ART group.

CONCLUSION: Although TB was a significant problem in ALHIV, timely administration of ART and IPT had a significant protective effect.

KEY WORDS: TB incidence; INH preventive therapy; pre-ART

TUBERCULOSIS (TB) is a global public health problem, with about 9 million new infections and 1.5 million deaths annually.[1] People living with the human immunodeficiency virus (PLHIV) comprise 13% of all TB deaths. However, data on the contribution of TB in adolescents to the global TB burden are limited. Lack of adolescent-specific health data is a global challenge.[2] Older epidemiological data suggest increased TB incidence during adolescence,[3,4] with the risk of TB being highest during infancy and adolescence.[5–7] More recent data suggested high TB prevalence among adolescents aged 12–18 years.[8]

As adolescents are socially active, and risk factors such as smoking, substance use and stress are more common in this group, their potential to transmit to their peers is high.[9–11] Furthermore, with increasing numbers of perinatally HIV-infected children reaching adolescence, it is important to have a clearer understanding of both the magnitude and factors contributing to TB incidence in this age group to be able to plan appropriate preventive measures.[10,11]

Data on the magnitude and determinants of TB among adolescents are scarce, and when they are reported they do not generally focus on adolescents living with HIV (ALHIV) or report separately on the 10–19 years age group.[8,12–14]

Our objective was to determine the magnitude of TB among adolescents at each phase of the HIV care cascade in an ALHIV cohort 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;

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however, most HIV patients were concentrated in urban areas even in SNNPR. The eight health facilities were selected based on the high ALHIV population, according to the investigators' prior knowledge about the sites. Despite the considerable progress made in preventing and controlling HIV and TB, Ethiopia remains a high HIV and TB burden country.[1,16]

Study design

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

In accordance with national guidelines, all ALHIV were screened for TB symptoms at baseline and then at each clinic visit. Symptomatic patients underwent further clinical evaluation and diagnostic tests. The first-line diagnostic test during the cohort period was conventional sputum microscopy. Selected cases underwent chest radiography on physician recommendation. Rapid TB diagnostic tests were not part of the national guidelines at the time of enrolment.[17]

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

Data collection and management

Patient charts and registers were used 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, a paediatrician 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 checking and secure storage. A centrally based data clerk entered data from the checked, approved data abstraction forms into Statistical Package for the Social Sciences, version 22.0 (IBM Corp, Armonk, NY, USA). 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 in the standard operating procedures of the study protocol. The principal author performed random checks of the completed data abstraction forms at regular intervals.

Definitions

The main outcome variable was TB diagnosis during follow-up as confirmed and recorded in patient registers according to the national guidelines by the treating clinician.[18] Patients in whom TB diagnosis was confirmed at least 4 weeks after the patient was in pre-ART care, but before the ART start date, were defined as having pre-ART TB. Patients who developed TB after 4 weeks of ART initiation were considered to have TB during ART.

We determined completion rates for isoniazid preventive therapy (IPT) from patient registers. Those who completed a 6-month course of IPT and were confirmed by clinicians as such were considered 'completed', those who received IPT for <6 months were categorised under 'did not complete', and those with missing information were recorded as 'no information'.

Information on adherence to cotrimoxazole therapy (CPT) was also retrieved from patient registers. Clinicians recorded either 'good' or 'poor' based on patient self-report. We determined adherence status as per the clinician's record at the time of the patient's last visit.

Data analysis

Data analysis was performed using SPSS version 22. TB incidence rate was calculated as the number of new episodes of TB per 100 person-years of observation (PYO). 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. Other variables included were baseline WHO clinical stage, CD4 count (categorised as <350 vs. $\geqslant 350$ cells/μl for the pre-ART cohort and <200 vs. $\geqslant 200$ cells/μl for the ART cohort), history of cough of >2 weeks, and IPT (ever used or not). Covariates included sex and address (as urban or rural) in the Cox model. Covariates with a P value of <0.25 in the univariate model were included in the multivariate model. Two-sided $P < 0.05$ was considered statistically significant.

Ethics

The National Research Ethics Review Committee, Addis Ababa, the Regional Health Bureau Ethical

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

Characteristic	*n* (%)
Region	
SNNPR	582 (54.3)
Addis Ababa	490 (45.7)
Total	1072 (100)
Median age, years	13
Female sex	644 (60.1)
WHO stage	
I–II	501 (46.7)
III–IV	544 (50.7)
Missing	27 (2.5)
Total	1072 (100)
CD4 count cells/μl, median [IQR]	228 [106–410]

HIV = human immunodeficiency virus; SNNPR = Southern Nations', Nationalities' and Peoples' Region; WHO = World Health Organization; IQR = interquartile range.

Review Committee, Hawassa, and the Institutional review Board of the College of Health Sciences, Addis Ababa University, Addis Ababa, approved the protocol. All research staff were trained in the ethical conduct of human subjects research. Measures to protect data security and confidentiality are described above.

RESULTS

Baseline characteristics

Of 1221 adolescents screened, 1072 who fulfilled the eligibility criteria 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 the median CD4 count was 228 cells/μl. Table 1 gives the 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 a full course of IPT, 22 (15.5%) did not complete IPT, and information was missing for 17 (12%); 84.5% of adolescents received CPT, 68.9% of whom were reported as having a good CPT adherence rate at their last visit.

Tuberculosis 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 enrolment, 50.3% of whom 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, 46% of whom had a previous history of TB at baseline. TB incidence was 16.32/100 PYO (95% confidence interval [CI] 13.75–19.24).

Having advanced WHO clinical stage (adjusted hazard ratio [aHR] 5.68, 95%CI 3.72–8.68), CD4 count <350 cells/μl 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) were predictive of TB.

Table 2 Cox regression analyses of predictors of pre-ART TB incidence in adolescents living with HIV, Ethiopia, 2005–2013

Variable	Incident TB case	PY	Incidence/100 PYO	HR (95%CI)	aHR (95%CI)
Region					
Addis Ababa	69	437.51	15.77 (12.27–19.96)	Reference	Reference
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)	Reference	Reference
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)	Reference	Reference
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)	Reference	Reference
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, cells/μl*					
⩾350	42	573.36	7.32 (5.35–9.81)	Reference	Reference
<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)	Reference	Reference
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)	Reference	Reference
Yes	66	84.84	77.78 (60.16–98.97)	6.23 (4.45–8.69)	2.22 (1.51–3.26)

* Numbers do not total 142 because of missing data.
ART = antiretroviral therapy; TB = tuberculosis; HIV = human immunodeficiency virus; PY = person-years; PYO = PY of observation; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; SNNPR = Southern Nations, Nationalities, and Peoples' Region; WHO = World Health Organization; IPT = isoniazid preventive therapy.

Table 3 Cox regression analyses of factors associated with TB incidence rate after ART, Ethiopia, 2005–2013

Variable	Incident TB case	PY	Incidence/100 PYO	HR (95%CI)	aHR (95%CI)
Region					
Addis Ababa	40	2009.76	1.99 (1.44–2.68)	Reference	Reference
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)	Reference	Reference
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)	Reference	Reference
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)	Reference	Reference
III–IV	51	2039.84	2.50 (1.88–3.26)	1.21 (0.64–2.31)	1.23 (0.63–2.38)
CD4 count, cells/μl					
⩾200	16	1034.02	0.9 (0.51–1.46)	Reference	Reference
<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)	Reference	Reference
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)	Reference	Reference
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 total 64 because of missing data.
TB = tuberculosis; ART = antiretroviral therapy; PY = person-years; PYO = PY of observation; HR = hazard ratio; CI = confidence interval; aHR = adjusted HR; SNNPR = Southern Nations', Nationalities', and Peoples' Region; WHO = World Health Organization; IPT = isoniazid preventive therapy.

IPT was associated with a reduction in TB incidence, but this was not statistically significant (aHR 0.55, 95%CI 0.16–1.91; Table 2).

Tuberculosis after ART initiation

Of 816 patients placed on ART, 98 were on anti-tuberculosis treatment at ART initiation, including 58 in the intensive and 40 in the continuation phases of treatment. Furthermore, 64 patients developed TB during 2843.53 PYO, yielding a TB incidence rate of 2.25/100 PYO (95%CI 1.78–2.86) after ART initiation. Incidence rate was highest during the first year of ART (16.7/100 PYO) compared with 2.3 and 1.6/100 PYO at between 1 and 5 years and >5 years, respectively. Being in advanced WHO clinical stage (aHR 1.23, 95%CI 0.63–2.38), having a CD4 count <200 cells/μl 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. IPT use was associated with significantly lower TB incidence rate (aHR 0.06, 95%CI 0.01–0.45). Table 3 summarises the results for the ART cohort.

DISCUSSION

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

Both the pre-ART and the after ART TB rates in our cohort are at least 10 times higher than those reported among non-HIV-infected adolescents. In rural Uganda, for example, TB incidence among adolescents aged 12–18 years was 0.235/100 PYO,[13] while among adolescents in a South African school, incidence was 0.45/100 PYO.[19]

Pre-ART TB incidence in our study was higher than that reported in adult cohorts from similar settings. In two reports from southern Ethiopia, pre-ART TB incidence ranged from 9.9 to 11.1/100 PYO.[20,21] However, overall TB incidence of 2.25/100 PYO in adolescents who received ART in our study was lower than the rate of 3.7/100 PYO in an adult cohort reported from southern Ethiopia.[21] In Addis Ababa, TB incidence was 3.1/100 PYO in an adult cohort of patients on ART.[22] In a South African adult cohort, incidence declined from 3.5 in the first year to 1.01/100 PYO in the fifth year.[23] The heightened risk of TB among adolescents in the current study despite improved TB prevention and control efforts in Ethiopia is a clear indication of the need to prioritise ALHIV as key populations for TB prevention.[1]

The predictive value of CD4 count and WHO clinical stage are well documented in adult cohorts.[18,24] We found similar results in the pre-ART cohort, but we did not find a 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 than 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.[18]

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

Previous history of TB was associated with more than double the risk of TB in this cohort. Earlier studies among adult cohorts reported conflicting results,[23,28] but a more recent study from Brazil reported a two-fold risk of TB in patients with a previous history of TB; about 38% of the patients in that report had previous history of TB.[25] In our cohort, about 46% of patients who developed TB during pre-ART follow-up had a 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.[26,27] As our cohort included patients from the pre-ART era over a decade before, 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 routine screening in high TB-HIV burden settings.

Our study had some limitations. TB diagnosis was based on microscopy or radiography, potentially leading to the underestimation of incident TB cases because of the low sensitivity of the diagnostic method. Due to the retrospective method of data collection, 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 they will likely have broader implications with the 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. Although IPT and ART had a protective effect, IPT coverage was unacceptably low in this age group. The first year of ART was the period with the highest rates of incident TB cases, followed by the pre-ART period. TB programmes should prioritise ALHIV as a target group for TB prevention and control efforts, especially during the pre-ART period up to the first year after ART. Ensuring adequate IPT and ART coverage should be considered urgent priorities. Disaggregating routine TB data by adolescent age group can provide more information about TB in adolescents. Moreover, prospective studies with more comprehensive variables will provide further insights about the magnitude and predictors of TB in this age group.

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RESUME

CONTEXTE : Huit structures de santé dans deux régions d'Ethiopie.

OBJECTIF : Déterminer les taux d'incidence de la tuberculose (TB) et les facteurs associés parmi des adolescents vivant avec le virus de l'immunodéficience humaine (ALHIV) dans des structures de santé sélectionnées en Ethiopie.

SCHÉMA : Ceci a été une étude rétrospective de cohorte. Les ALHIV enrôlés dans la prise en charge du VIH entre janvier 2005 et le 31 décembre 2013 ont constitué la population d'étude. La principale variable étudiée a été le diagnostic de TB pendant le suivi. Les principales variables indépendantes ont été le stade clinique initial de l'Organisation Mondiale de la Santé (OMS), le nombre de CD4, des antécédents de TB et l'utilisation du traitement préventif par isoniazide (IPT). Nous avons estimé les taux d'incidence de la TB comme le nombre de cas par 100 années-personne d'observation (PYO). L'analyse de régression de Cox a permis de contrôler les facteurs de confusion.

RÉSULTATS : Sur 1221 adolescents dépistés, 1072 adolescents éligibles ont été étudiés ; 60,1% étaient des filles. Le taux d'incidence de la TB a été de 16,32 par 100 PYO pendant la période de suivi précédant le traitement antirétroviral (pré ART), mais a décliné à 2,25 par 100 PY après la mise en route de l'ART. Un stade clinique OMS avancé (ratio de risque ajusté [aHR] 2,71 ; IC95% 1,69–4,33) et le nombre de CD4 <350 cellules/µl (aHR 2,28 ; IC95% 1,10–4,81) ont prédit l'incidence de la TB dans la cohorte pré ART. L'utilisation de l'IPT a été associée à une réduction significative de l'incidence de la TB dans la cohorte sous ART, mais pas dans le groupe pré ART.

CONCLUSION : La TB a été un problème significatif chez les ALHIV dans les structures de santé de l'étude en Ethiopie et encore davantage pendant le suivi pré ART et au début de l'ART. Les adolescents devraient être une cible prioritaire des mesures de prévention de la TB, notamment de la mise en route rapide à la fois de l'ART et de l'IPT.

RESUMEN

MARCO DE REFERENCIA: Ocho establecimientos de salud en dos regiones de Etiopía.

OBJETIVO: Determinar las tasas de incidencia de tuberculosis (TB) y los factores asociados con la enfermedad en los adolescentes positivos frente al virus de la inmunodeficiencia humana (ALVIH), en varios establecimientos de salud escogidos de Etiopía.

MÉTODO: Fue este un estudio retrospectivo de cohortes. La población del estudio consistió en los ALHIV inscritos en la atención de la infección por el VIH de enero del 2005 al 31 de diciembre del 2013. El principal criterio de valoración fue el diagnóstico de TB durante el seguimiento. Las principales variables independientes fueron el estadío clínico de la infección según los criterios de la Organización Mundial de la Salud (OMS), el recuento de linfocitos CD4, el antecedente de TB y la administración del tratamiento preventivo con isoniazida (IPT). Se calcularon las tasas de incidencia de TB como número de casos nuevos por 100 años-persona durante la observación (PYO). Se aplicó un análisis de regresión de Cox a fin de ajustar los factores de confusión.

RESULTADOS: De los 1221 ALHIV tamizados, 1072 cumplieron con los criterios de inclusión del estudio, de los cuales el 60,1% era de sexo femenino. La tasa de incidencia de TB fue 16,32 por 100 PY durante el seguimiento antes de iniciar el tratamiento antirretrovírico (pre ART) y disminuyó a 2,25 por 100 PY después del comienzo del ART. Los factores pronósticos de la incidencia de TB en la cohorte de seguimiento antes del ART fueron un estadío avanzado de la infección por el VIH según la OMS (razón de riesgos instantáneos ajustada [aHR] 2,71; IC95% 1,69–4,33) y un recuento de linfocitos CD4 <350 células/µl (aHR 2,28; IC95% 1,10–4,81). La administración del IPT se asoció con una disminución considerable de la incidencia de TB en la cohorte que recibía ART, pero no en el grupo estudiado antes de iniciarlo.

CONCLUSIÓN: La TB representa un importante problema en los ALHIV de los establecimientos de salud de Etiopía que participaron en el estudio y, aun más, antes de iniciar el ART y al comienzo del mismo. Es preciso que al introducir las medidas de prevención de la TB se dé prioridad a los adolescentes, además de procurar el comienzo oportuno del ART y del IPT.