

Associated Factories and Time to Occurrence of Tuberculosis Among Children on HIV/AIDS Care in Assosa and Pawe General Hospitals North West Ethiopia: A Retrospective Cohort Study 2020

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Abstract

Background: Tuberculosis (TB) incidence in paediatrics and children living with human immune-deficiency virus (HIV) is an emerging global concern. Although, the incidence of TB among adult HIV patients is exhaustively studied in Ethiopia, but among children on HIV/AIDS care is overlooked. Knowledge of the time when TB develops during successive follow up could be helpful for time relevant intervention strategies.

Methods: health institution based retrospective cohort study conducted among 421 children on HIV/AIDS from 2009-2018. Time to develop TB was defined as time from enrollment for ART care until development of TB among children on ART. Proportional hazard assumption was checked for each variable and no variable was found with Schoenfeld test <0.05 . Variables with P -value <0.25 at bivariate Cox regression analysis were entered into multivariable Cox model. Multivariable Cox regression model with 95%CI and AHR was used to identify significant predictor variables to develop TB at $P < 0.05$.

Result: Totally 421 children were followed for a total of 662.5 Person Years of observation (PYO). The maximum and minimum follow up time on ART was 0.37 and 4.49 years, respectively. The median age of the children on ART at enrollment was 8 years (IQR=2-15). The Overall incidence density of tuberculosis in HIV infected children was 9.6/ 100 PYOs 95%CI (8.06-10.3). Tuberculosis occurrence among HIV infected children was significantly associated within TB history of contact AHR=3.7, 95%CI (2.89-7.2), not started on cotrimoxazole(CPT) AHR=2.4: 95%CI (1.84-4.74), incomplete vaccination AHR=2.4, 95%CI (1.32-4.5), sever stunting AHR =2.99:95%CI (1.2-7.81), having hemoglobin (Hgb) ≤ 10 mg/dl AHR = 4.02, 95%CI (2.01-8.1).

Conclusion: More than 80% of TB incidences occurred during two years of follow up after ART started. So intensified screening of CPT& therapeutic feeding is highly recommended for all children.

Introduction

The intricate linkage of tuberculosis(TB) with HIV infection for the past three decades become major threat and hindrance for international public health effort to achieve Millennium development goal [1]. Globally, tremendous progress has been made over the past decades in diagnosing and treating of TB and achieved 2% per year new TB incidence reductions [2]. However, in 2017 6.4 million new incidence cases of TB were reported [3], among this 9% (0.3 million) were new incidence of TB-HIV co-infections and 50% of new infection including inborn seropositive children were located in resource limited settings [4]. It is mainly due to difficulty in timely addressing prophylaxis and ART treatment gaps [5]. On the other hand, absence of sophisticated early HIV diagnosis technologies for inborn HIV infected children [6] increase early mortality by lethal opportunistic infections ,the commonest one is tuberculosis [7, 8]. It is one of the leading lethal opportunistic infection with 30–40% lifetime incidence risk for seropositive children [9, 10]. Global systemic review and meta-analysis on incidence of tuberculosis on people living with HIV/AIDS(PLWHV) in 2013 indicated, the incidence burden has variation in continental perspective

[11], which is 31.25% in African countries, 25.06% in Latin America countries, 17.21% in Asian countries, 20.11% in European countries, and 14.84% in the USA [12]. Several studies in African countries have shown that the incidence of TB among HIV positive children ranges from 1- 9.9 per 100 person years [9–11, 13] with different times of immunological and pathophysiological response for tuberculosis incidence [14, 15]. For instance tuberculosis occurrence in, Uganda & Zimbabwe 1.9/100 P-Y [11], Tanzania 5.2/100 P-Y [10]. According to global TB report of 2018, Ethiopia found top 17 twine TB & HIV epidemic countries with 8.6–17/1000 new TB incident including seropositive children [3], With each year, 3900 HIV infected children develop morbidity by opportunistic infection especially by TB [15]. Childhood TB incidence during successive follow up varied in different regions and health institutions in Ethiopia [16]. For example, in Adama 6.03/100 P-Y [17], Debre Markos 2.63/100P-Y [18], Gondar 4.9/ 100 PY [19], Northern Ethiopia 4.2 / 100 P-Y [20] and southern Ethiopia 2.6 /100 P-Y [21]. On the other hand, factors associated with TB incidence were identified [17–19, 22]. Notably ,functional status [20] WHO stage& anemia [20, 23], residence[20], nutrition status [17] adherence status [18]. Currently, tuberculosis incidence among seropositive children is an emerging and global concern, in fact due to its one of leading lethal opportunistic infections [24]. Although, studies have been conducted on TB incidence among children on HIV/AIDS care in Ethiopia [4] ,however the time of TB occurrence among on HIV/AIDS care children is incompletely described and overlooked [20, 25]. In addition, information on the time when TB develops is scarce [11, 19]. The main aim of this research is to assess Associated Factors and Time to occurrence of Tuberculosis among seropositive children in Assosa and Pawe General Hospitals North West Ethiopia.

Methods

Study area, design and population

We conducted health institutions based retrospective cohort study among 421 children on HIV/AIDS care from January 1st/2009 to December 31 /2018 at Assosa & Pawe general hospitals in Benishangule Gumuz regions. Both hospitals are located in this regional state in North West Ethiopia. This region is one of the nine regions in Ethiopia. Assosa is the capital city of this region and it is located at a distance of 659 km in west of Addis Ababa and Pawe hospital is also located a distance from 565 km from Addis Ababa in North West direction. This region has currently 2 general and 3 primary hospitals with one regional laboratory. This two selected Hospitals are routinely diagnose and treat tuberculosis based on the clinical findings, chest x-ray, AFB and XpertTB for suspected TB patients [26]. In both general hospitals there has been given ART care service 2007 pediatric HIV/AIDS guideline [27]. Following the time of enrollment to ART care continuum, all children have started ARV at both hospitals. Among these, 238 and 191 children were on follow up and care at Assosa general hospitals and Pawe general hospitals, respectively. From the registration log book, eight children with incomplete outcome data were excluded from the study.

Sample size determination and sampling procedure

Sample size for this study was calculated by using EPI INFO software using the following parameters. **A)** (a) of 5%, power 80%, Z = within 95% CI = 1.96 and AHR = 2.39 [20] (P1) = 6.6% and (P2) = 15.8% obtained

408 by adding 5% incomplete data final sample size will be 421. Computer generated random number used for final study subject of study subject from two hospitals.

Totally there existed 1230 children started HIV/AIDS care and registered for SMART data care since January 1st /2009–31st December 2018. Since in Assosa general hospitals 723 and Pawe general hospitals 507 children started HIV/AIDS care and proportionally sample allocation is used based on their source population for 421 final sample sizes.

$$\begin{array}{l} \text{Assosa Hospital} \\ \text{N} \end{array} \quad \begin{array}{l} n_{i1} = \frac{(N_2)n}{N} = \frac{(421)(723)}{1230} = 247 \\ \text{N} \quad 1230 \end{array} \quad \begin{array}{l} \text{Pawe Hospitals} \\ \text{N} \end{array} \quad \begin{array}{l} n_{i2} = \frac{(N_2)n}{N} = \frac{(507)(421)}{1230} = 174 \\ \text{N} \quad 1230 \end{array}$$

First by using Unique ART number of each individual card retrieved from SMART data set of pediatrics ward. Then by using computer generated random number 247 study participants from Assosa hospitals and 174 study participants from pawe general hospitals were recruited.

Study variables

In this study, the outcome variable was Time to develop TB; Incident TB cases were only those who developed new TB (EPTB & PTB) during the follow up period. The outcome variables ascertained if TB occurred only after started ART during ART follow up times.

Independent variables included: Age of children, sex, residence, family size, WHO clinical stage TB contact history, CD4 counts, Hgb, functional status, Isoniazid preventive therapy, Cotrimoxazoles preventive therapy, vaccination status, weight for age (under nutrition), weight -for -height (wasting) and height –for –age (stunting).

Operational definitions

Case ascertainment: The outcome variables (TB) was diagnosed based on bacteriological, molecular, histopathology and clinical methods by using (microscope, sputum culture, chest x-ray, and Xpert or combinations) during patient presentation for TB symptoms [28].

Event: New occurrence of tuberculosis during HIV/AIDS care follows up times with study in periods.

Censored: HIV positive children who did not developed TB during HIV/AIDS follow up.

TB history of contact: Children during ART follow up before TB incidence developed, having history of survives or contact at any time with who has active PTB patient.

Opportunistic infection: for HIV infected children during the following if any one of diseased developed registered on ART follow up form by their code (BP = Bacterial pneumonia ,UL = oral ulcer, Z = Herpes zoster, PCP = pneumocystis carnie pneumonia ,DC/DA –chronic / acute diarrhea, CT = central nervous toxoplasmosis CM streptococcal meningitis [29].

CD4 :was classified as below the threshold according to the following age-specific thresholds: less than 15% for children aged 12–35 months, less than 10% for children aged 36–59 months or less than 100 cells/mm³ for children aged 5–15 years [20].

Stunting, underweight and wasting: The child being 2 standard deviations (SDs) below the normal for height for age, weight for age, or weight for height, according to the WHO 2006 curve. For children under or equal age 2, wasting was measured by weight for length Z-score; for children above age 2, wasting was defined by Z-score. Z-score ≥ -2 was defined as non-wasting; $-3 \leq Z\text{-score} \leq -2$ was defined as moderate wasting; Z-score ≤ -3 was defined as severe wasting. Stunting was measured by height/length for age Z-score. Z-score ≥ -2 was defined as non- stunting; $-3 \leq Z\text{-score} \leq -2$ was defined as moderate stunting; Z-score ≤ -3 was defined as severe stunting [10, 17, 22].

Data collection tools, procedures, and quality control

Four bachelor nurses and two supervisors were selected for data collection processes and all had took ART training. For quality of data collection process, one-day traing was given in two hospitals with two supervisors for data collectors. The principal investigator and two supervisor followed data. Data were collected using the data abstraction tool and medical history sheet prepared from Ethiopian Federal ministry of health HIV/AIDS follow up forms [15].

Data processing and analysis

Data entered into the computer using EPI-DATA version 3.1 & exported to STATA 14.1 for cleaning and analysis. Descriptive analysis, such as tables, graphs, Kaplan Meier survival curve and log rank test was done. Hazard ratio with 95%CI & $P \leq 0.05$ was used to measure association with independent variable. The overall survival graph and hazard failure estimated curve was used to show survival and hazed probability of risk group. Cox-regression model was fitted to identify predictors for incidence of pulmonary tuberculosis. All predictors that was associated with the outcome variables in the bivariable analysis at a hazard ratio of P-value 0.25 or lower was included in multi variable Cox-regression model. Variables with adjusted hazard ratio in multivariable Cox-regression with their corresponding 95% confidence interval with P-value < 0.05 was considered as significant predictors. Cox–proportional hazard assumption was checked by (log-log plot) & expected versus observed Kaplan Meier graph test for each variable with schoenfield residuals test for each variable. No variables less than < 0.05 .After multivariable cox regression was built by transforming from bivariable $P < 0.25$, for finally model selection was selected by AIC & BIC criteria [30].Finally, model adequacy was checked by Nelson Alana and Cox Snell residual combination was used for checked model adequacy & it became on straight line with Zero origin in X and Y axis.

Result

Demographic characteristics of study participants

From 429-study participant, 421 were included for final analysis and 8 cards were discarded due to incompleteness. The median age of children during this time was 9 years with (IQR = 2–15). More than one-third 39.5% of children were found at 6–10 years age classification group. Slightly more than half 51.54% of children were female in sex, of them 52% were live in rural residence. Among the total study participant children 54.87% of them lived with 3–4 family groups among 56.06% seropositive children lived with their family.

Baseline clinical characteristic

Nearly two- third (62.5%) of study participants were addressed isoniazid. Regardless of HAART initiation after starting HIV/AIDS care in both hospital 126(29.5%) children develops opportunistic infection. The most common opportunistic infection was identified, bacterial Pneumonia 53(35.9%) & Pneumocystis carnie pneumonia (PCP) 27(21.6%) respectively. More than two third of children (63.9%) found WHO clinical stage 3&4. Among total study participant 147(34.92%) has hemoglobin \leq 10 mg/dl. From the total, two-third of children 276 (66.27%) were completed their vaccinating.

Similarly nearly one fourth of 113(26.84%) HIV infected children CD4 count was below threshold level .Eighty percent of the children (80.24%)has good functional status progression. Among the total study participants, 56(13.4%) has poor ART adherence. During the follow up times from 421 total study participants 199(47.8%) has on children cohort of follow up, 20(4.75%) drop totally from the follow up [Table 1].

Table 1

Base line socio demographic, clinical and laboratory characteristics of children on ART care at Assosa and Pawe General Hospitals since January 2009 – December 2018 EC

Variables	Frequency	Percent
	N = 421	100%
Sex Male	204	48.46
Female	217	51.54
Age <=5 years	87	20.67
6–10	146	34.39
>=11 years	188	43.94
Residence Urban	205	48.69
Rural	216	51.31
Hemoglobin >10 mg/dl	263	62.92
<=10 mg/dl	158	37.92
WHO stage 1&2	269	63.9
Stage 3%4	152	36.10
CD4 count Below threshold	113	26.84
Above threshold	308	73.16
Functional Appropriate	338	80.24
Delay	50	11.89
Regression	31	7.84
Adherence Good	224	57.96
Fair	121	28.73
poor	56	13.44
Isoniazid yes	258	61.52
No	163	38.48
Cotrimoxazoles yes	321	76.26
No	100	23.94
opportunistic infections yes	126	29.93
No	295	70.07

Variables	Frequency	Percent
	N = 421	100%
Vaccination Completed	276	66.27
Defaulted	76	18.2
Not registered	69	16.05
TB contact history Yes	135	32.8
No	286	68.17
Family size <=2	133	31.83
3-4	219	52.21
5-6	50	11.88
>=7	19	4.09
Children status being on follow up	199	47.7
Lost from follow up	43	10.23
Transfer in to adult	91	21.62
Transfer out	56	13.30
Died	12	2.85
Drop	20	4.75
ART regiment Changed	85	20.24
Not changed	336	79.2

Baseline Nutritional status of HIV infected children

From the total 421 study participant, 33 (7.84%) children developed sever stunting (HFA<-3 Z score), also 72 (17.10%) study participant developed moderate wasting (HFA) between - 3- -2 Z score finally 313 (74.35%) HIV infected children remain above >-2 Z score.

Tuberculosis incidences rate

At the end of the follow up periods, 667.7 Person Years (PYOs) of observation was obtained. During this time 64 new TB incidences occurred, of this 30 were pulmonary tuberculosis and the remaining 34 were extra pulmonary tuberculosis. The cumulative incidence rate 64 TB case found (15.64%) occurred. Totally, 64-event alone took 88.2 PYOs of observation taking during follow up. The overall incidence density of tuberculosis was found 9.6 person/100 years 95%CI (8.06–10.3).

Survival status of HIV infected children

Three hundred fifty-seven (84.79%) observation was censored at the end of the follow up times. During this time 556.8 Person- years of risk, time was observed with minimum and maximum of 0.39 and 4.5 years of observation obtained respectively [Table 2].

Table 2
summary of TB free survival rate of HIV infected children at Assosa and Pawe General Hospitals since 2009–2018

Time in years/month	Survival rate	95%CI	New events	Cumulative frequency	Frequency %
1 years	96.04%	93.62–97.56	20	20	31.3%
2 years	82.62%	77.80–86.49	33	53	82.3%
3 years	77.65%	71.57–82.59	10	63	98.1%
4 years	68.92%	53.32 –80.22	1	64	100%
≥ 5 years	68.92%	53.3– 80.2	0	64	100%

Predictors for Tuberculosis

During bivariabes analysis totally 16 variables were selected in the first steps of model building and 10 variable selected, as the best model by comparing their model Asian information criteria (AIC) and Bayesians information criteria (BIC), which include (age, isoniazid preventive therapy, Cotrimoxazole preventive therapy, TB history of contact, vaccination status, height for age, who clinical stage, CD4 count, Hemoglobin, adherence) involved in multivariable analysis. Five of among predictors, TB history of contact, not started on cotrimoxazole. Incomplete vaccination, sever stunting, having Hemoglobin \leq 10 mg/dl were found have statically significant with outcome variables [Figure2].Based on this, the risks of developing TB among HIV infected children for not started cortimoxazole is 2.4 times increase as compared with taking cotrimoxazole (AHR = 2.4:95%CI ,1.84–4.74) [Table 3].

Table 3

Bivariable and multi variable cox-proportional hazard analysis for predictors of TB among children treated on ART OPD at Assosa and Pawe General Hospitals 2009–2018

Survival status of children				Multivariable cox regression	
Variables	TB incidence	Censored	CHR 95% CI	P-value	AHR = 95% CI
Age of children < =5 years	2	85	1		
6–10 years	12	134	3.4 (0.7 15.52)	0.68	1.38 (0.28 6.6)
>=11 years	50	138	12.(12.7 49.6)	0.12	2.89 (0.62 12.)
Isoniazid yes	15	243	1		1
No	49	114	6.58(3.6 11.7)	0.80	0.91(0 .41 1.9)
Cotrimoxazoles yes	28	293	1		1
No	36	64	4.7(2.87 7.75)	0.003	2.5 (1.4 4.74)*
TB history of contact Yes	53	82	12.21(6.6 23.4)	0.002	3.7 (2.89 7.2)*
No	11	275	1		1
Vaccination status Complete	23	253	1		1
Default	33	43	5.75(3.4, 9.72)	0.005	2.6(1.32 4.5)*
Not registered	8	61	1.24(0.5, 2.87)	0.25	1.68 (0.66 4.1)
CD4 count Above threshold	28	280	1		1
Below threshold	36	77	1.58(0.91 2.74)	0.403	0.72(0.37, 1.42)
Adherence Good	21	223			1
Fair	15	104	1.9(0..89 4.07)	0.817	1.2(0.48, 2.94)
Poor	28	30	7.1(0.37 26.32)	0.746	1.19(0.52 2.71)
Height for age (HFA) Normal	35	249	1		1

Survival status of children			Multivariable cox regression		
Moderate	21	83	1.64(0.95 2.82)	0.06	1.32(0.62 2.71)
Sever stunting	8	25	1.93(0.89 4.1)	0.03	2.96(1.2 7.88)*
WHO stage 1&2	14	255	1		1
Stage 3&4	50	102	9.1(4.9 16.4)	0.07	2.1 (0.99. 4.48)
Hemoglobin > 10 mg/dl	12	251	1		1
< =10 mg/dl	52	106	9.62(5.13 18.0)	0.001	4.02 (2.1 8.1)*

The risks of developing TB among HIV infected children having previous TB history of contact is 3.8 times increased as compared with no previous TB history of contact (AHR = 3.8: 95%CI, 2.89–7.2). The risks of developing TB among HIV infected children having incomplete vaccination was 2.4 times increase as compared with completed vaccination during their life time (AHR = 2.4: 95%CI,1.32–4.5). The risks of developing TB among HIV infected children having Sever stunting 2.99 times increase as compared with HIV infected children having normal height for their age (AHR = 2.99:95%CI ,1.2–7.81). The risks of developing TB among HIV infected children having Hemoglobin \leq 10 mg/dl times increase as Compared with hemoglobin \geq 10 mg/dl (AHR = 4.02:95%CI,2.01–8.1).Model adequacy of this multivariable cox regression was checked by Nelson Alan and Cox Snell residual combination test. [Figur3].

Discussion

The finding of this study indicated that the overall incidence of tuberculosis was found 9.6/ 100 Person per years (PYOs) 95%CI (8.06–10.39). This is not comparable with study finding in southern Ethiopia 2.6/ 100 PYOs[21], Debre Markos 2.63 /100 PYOs [18], Gonder 4.9/ 100 PYOs [19], Adama 6.03 /100 PYOs [17]. In fact the study area has predominant distribution of tuberculosis [26]. The finding of this study revealed that not started Cotrimoxazoles prophylaxis was independently associated with occurrence of TB. This is agreed with northern Ethiopia [20] Adama hospitals[17].This might be due to Cotrimoxazoles preventive therapy significantly reduces HIV related morbidity and mortality from lethal opportunistic infections [3]. On the same way, seropositive children having TB history of contact is associated with TB incidence. This is in line with south Africa[9].In fact lack of awareness about transmission of TB might easily acquire the infection from nearby active patients[33]. Also this study indicates; having incomplete vaccination was significantly associated with TB occurrence. This is similar with finding in Adama [17] and Gondar [19]. On the same way HIV infected children having sever stunting was independently

associated with incidence of TB .This in line with the study finding Tanzania[10] and Uganda & Zimbabwe [11]. The fact is human immune virus increases nutrient mal-absorption due to metabolic alterations that culminate in weight loss and stunting with time leads early exposed for opportunistic infections [29],this facilitate rapid viral replication consumed body energy and create arena for incidence of TB [2, 34].This study finding also showed that children having hemoglobin ≤ 10 mg/dl was independently associated with TB incidence as compared with hemoglobin level > 10 mg/dl having children. This is in line with the study finding in Adama hospitals [17],university of Gonder [19], Dar es Salaam, Tanzania[10], England and wales[23]. In fact hemoglobin levels had high predictive value for incident TB and death's ,and incidence TB is directly associated with severe anemia [35]. Regardless of starting HAART moderate or severe anemia can be independent predictor for TB [35, 36] .

Limitation of the study

Retrospective nature of this study is one of the limitations of this study .due to this some of clinical important predictor variable which has independently associated with incidence of TB occurrence in other studies like educational status of children, economic status of family were not included in these study.

Conclusion

Incidence of TB was an important medical problem for children living with HIV ART treated in both Hospitals. This study finding concluded that baseline not ever taking cotrimoxazoles ,having moderate stunting ,hemoglobin level lower than standard, incomplete vaccination ,having previous history of contact with TB has significantly and independently associated TB incidence. So intensified screening of cotrimoxazoles and malnutrition was highly recommended for intervention.

Abbreviations

AFB : Acide Fast Baccilli, AIDS: Acquired Immunodeficiency Syndrome; AHR: adjusted hazard ratio; ART: highly active antiretroviral therapy; CD4: Cluster of Differentiation 4; CI: confidence interval; EPTB ,extra pulmonary tuberculosis CPT: cotrimoxazoles prophylactic therapy,IPT isoniazid prophylaxis therapy, PTB pulmonary tuberculosis, PLWH: people living with HIV/AIDS, OIs: opportunistic infections; WFA= weight for age, HFA =height for age, WFH= weight for height WFH: Weight for Height, WFA: Weight for Age, HFA: Height for Age, PYOs: Person Years of Observations.

Declarations

Ethics statement

Ethical clearance was obtained from the ethical review committee of Debre Markos University, College of Health Sciences (Ref. No: HSC/984/16/12). A formal letter were submitted on both Assosa and Pawe general hospitals for permission to be done entitled research articles, Time to develop pulmonary

tuberculosis, predictors among HIV infected children receiving antiretroviral therapy, within two general hospitals, and permission was assured. All information collected from patient cards was kept strictly confidential and the names of patients were not included in the checklist. Confidentiality consent was not needed as it was a retrospective study was conducted on secondary data.

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Data availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Consent for publication

No consent for publication

Competing interests

The authors declare that they have no competing interests.

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Figures



MAP OF BENISHSANGULE GUMUZE REGIONAL STATES



Figure 1

Adapted from <https://www.Map of Benishangule Gumuz Regional state>. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

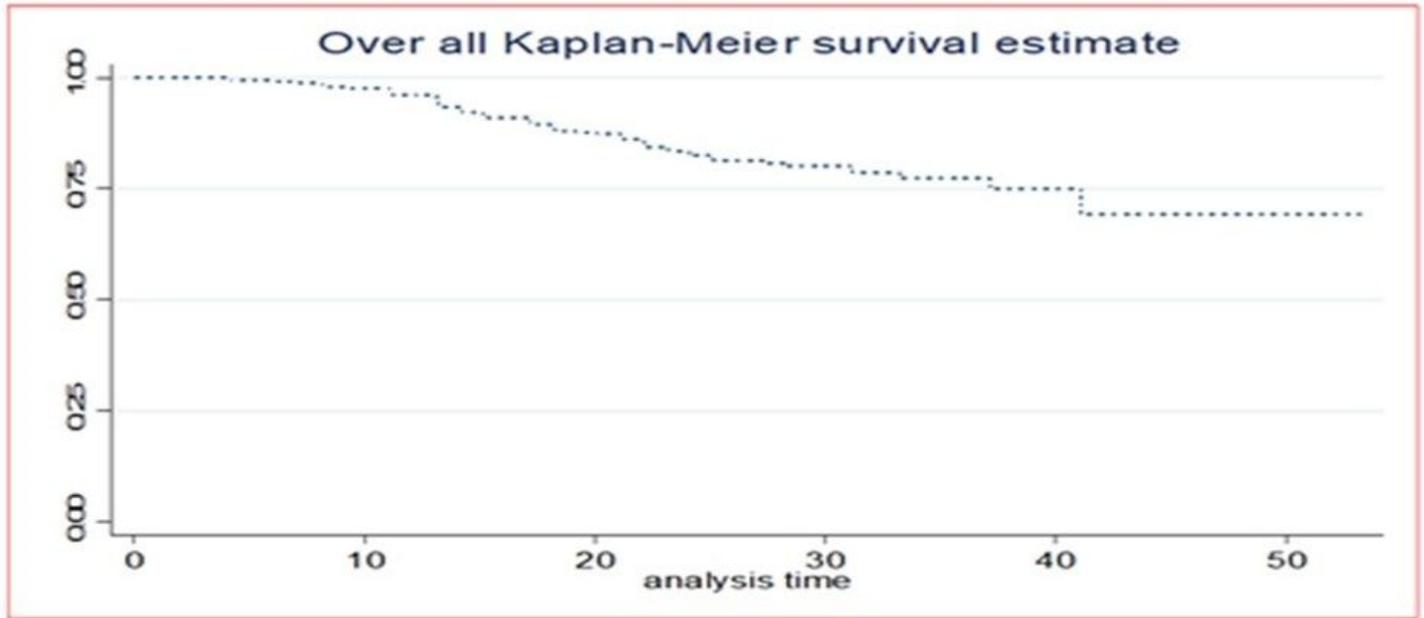


Figure 2

The overall Kaplan-Meier TB free survival probability of HIV infected children in two general hospitals since 2009-2018.

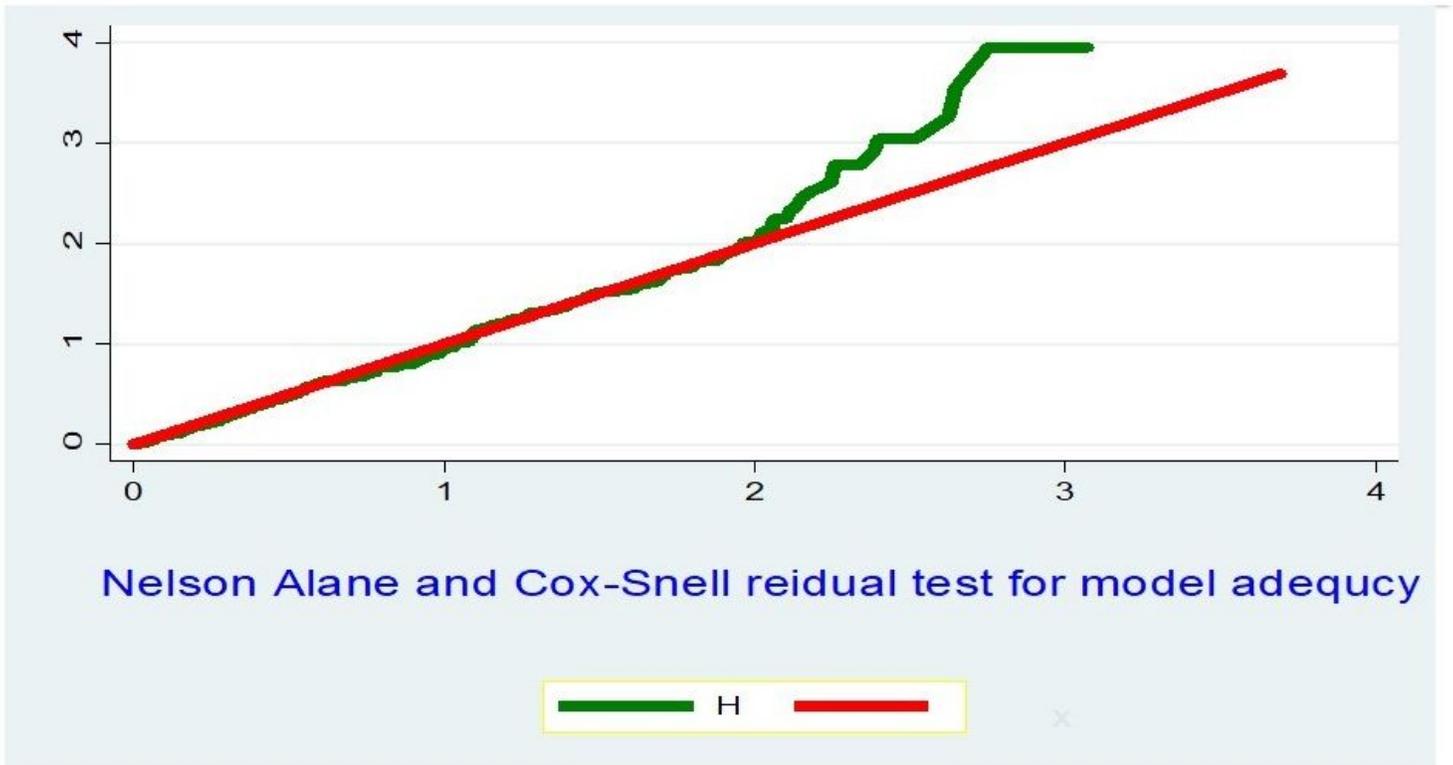


Figure 3

Final model adequacy checking by Nelson-Alone and Cox-Snell residual test after comparing multivariable-Cox regression models by AIC and BIC for titles of factors associated and time to occurrence of TB among HIV infected since 2009-2018