

Time to develop tuberculosis and predictors of incidence among anti-retroviral therapy children on two selected hospitals at benishangule Gumuz region, North West Ethiopia: A retrospective cohort study

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Abstract

Background: Currently, 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; the incidence of TB among children on ART is overlooked. Knowledge of the time when TB develops among children on ART could be helpful to develop time relevant intervention strategies.

Methods: This was a hospital based retrospective cohort study conducted among 429 children on ART 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: 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 9 years (SD=3.36). 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), severe 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 like TB [7, 8]. It is one of the leading lethal opportunistic infection with 30–40% lifetime incidence risk for HIV infected children [9, 10]. Global systemic review and meta-analysis on incidence of tuberculosis among PLWHIV 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 100PY [9-11, 13] with different times of immunological and pathophysiological response for tuberculosis incidence [14, 15], for instance in Uganda & Zimbabwe it was 1.9/100 P-Y [11] and in Tanzania it was 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 rate varied in Ethiopia among different regions and health institutions [16]. For example, in Adama it was 6.03/100 P-Y [17], in Debre Markos 2.63/100P-Y [18], in Gondar 4.9/ 100 PY [19], in Northern Ethiopia 4.2 / 100 P-Y [20] and southern Ethiopia 2.6 /100 P-Y [21]. Another studies indicated predictor for TB incidence during ART follow up time were identified [17-19, 22]. Mainly, bedridden functional status [20] WHO stage 3 & 4, not on ,anemia [20, 23], rural residence[20], under nutrition [17] poor adherence [18]. Currently, tuberculosis incidence in peadtrics and children is an emerging and global concern due to its one of leading lethal opportunistic infection for children living with HIV [24]. Although, studies have been conducted on TB incidence among children on ART near the major cities [4] , the incidence of TB among children on ART at rural and nomadic community is incompletely described and overlooked [20, 25]. In addition, information on the time when TB develops among children on ART is lacking too [11, 19].

Methods

Study area, design and population

We conducted a retrospective cohort study on 429 children on ART on treatment and care from January 1/2009 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 logbook, 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)** (α) 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 723 children started HAART and registered on computer SMART DATA sets of ART registration office since January 1st /2009 – 31st December 2018. Assosa hospitals 407 and Pawe general hospital 316 children were treated. There for proportionally allocated to selected 421 samples from two hospitals.

Assosa Hospital $n_{i1} = \frac{(N_2)n}{N} = \frac{(421)(407)}{723} = 236$

N **723**

Pawe Hospitals $n_{i2} = \frac{(N_2)n}{N} = \frac{(316)(421)}{723} = 185$

N **723**

First by using Unique ART number of each individual card retrieved from SMART DATA set of ART children ART office. Then by using computer generated random number 236 study participants from Assosa hospitals and 185 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].

Pulmonary tuberculosis: Pulmonary tuberculosis (PTB) refers to a case of TB involving the lung parenchyma. Military tuberculosis is also classified as pulmonary TB because there are lesions in the lungs. **Extra pulmonary tuberculosis (EPTB):** refers to a case of TB involving organs other than the lungs [28]. **Event:** New occurrence of tuberculosis during ART care follows up times with study in periods **Censored:** HIV positive children who did not developed TB during ART 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].

Seropositive: children <15 years were confirmed diagnosed of HIV /AIDS and under follow up.

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; $-3 \leq \text{Z-score} \leq -2$ 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; $-3 \leq \text{Z-score} \leq -2$ 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 training 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.

Results

Demographic and clinical characteristic 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 (SD= 3.66). Majority (39.5%) of children was found at the age of group of 6-10 years. slightly more than half (51.54%) of children were female in sex and 52% of children were live in rural residence. Nearly two third (62.5%) of study participants were addressed isoniazid and majority of (56.06%) children lived with their family. From the total study participants 126 children develop opportunistic infection. The most common opportunistic infection was bacterial Pneumonia 53(35.9%) & PCP 27(21.6%). More than two third of children (63.9%) found WHO clinical stage 3&4. Among total study participant 147(34.92%) has hemoglobin ≤ 10 mg/dl. Among 421 children, 231(54.87 %) participant lived in 3-4 family groups. Among the total study participants more than two-third were 276 (66.27%) were completed their vaccinating (**Figure 1**). On the same way among the total study participants, 113(26.84%) HIV infected children developed CD4 count below threshold level similarly 338(80.24%) children has appropriate developmental 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].

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. Among this 28 were found pulmonary tuberculosis and 33 were EPTB. 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 before event occurrence. The overall incidence density of tuberculosis among HIV infected children was 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.

[Table2]. 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 (**Figure 2**).

Predictors of tuberculosis

During bivariable analysis totally 16 variables were selected in the first steps of model building and 10 variable selected, as the best model by comparing log likelihood ratio, which include (age, isoniazid preventive therapy, Cotrimoxazole preventive therapy, TB history of contact, vaccination status, HT/WT, 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, severe stunting, having Hemoglobin ≤ 10 mg/dl were found have statically significant with outcome variables **[Figure3]**. Based on this, the risks of developing TB among HIV infected children for not started cotrimoxazole is 2.4 times increase as compared with taking cotrimoxazole (AHR=2.4:95%CI ,1.84-4.74) **[Table 3]**.

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). Moreover, HIV infected children didn't vaccinate in their life time has higher risks of developing TB. 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 Severe 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 ≤ 10 mg/dl times increase as compared with hemoglobin ≥ 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. (**Figure4**).

Discussion

To succeed WHO 2030 "End TB epidemic " strategies there must be collaborative working of TB program with HIV /AIDS patients to address sufficient prophylaxis and ART gap [3]. Accordingly, the finding of this study indicated that the overall incidence of tuberculosis in HIV infected children was found 9.6/ 100 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], Northern Ethiopia 4.2/ 100 PYOs [20], Gonder 4.9/ 100 PYOs [19], Adama 6.03 /100 PYOs [17]. This might be due to higher burden of tuberculosis in resource limited settings for early diagnosis and intervention[26]. The study finding in South Africa indicate that the incidence of TB in HIV children is as higher as 21.1/ 100PYO [9]. This might be due to south Africa was classified as twine TB/HIV epidemic incidence site [31, 32]. As time goes, incidence of TB in some settings lower been observed in recent times[20]. According to the finding, this study HIV infected children not started cotrimoxazoles during their follow up time was independently associated with incidence of TB as compared with taking cotrimoxazole. This is in line with north Ethiopia [20] Adama referral hospitals[17]. In fact it might be due to Cotrimoxazoles preventive therapy significantly reduces HIV

related morbidity and mortality of lethal infections [3]. On the same way, this study finding also showed that HIV infected children having previous TB history of contact is independently associated with incidence of TB as compared with non-TB contact children. This is in line with the study finding in south Africa[9].In fact low educational status and lack of awareness about transmission of pulmonary TB might easily acquire the infection from chronic carrier of nearby patients[33].

The finding of this this study indicated among HIV infected children having incomplete vaccination has independently associated with the risks of developing TB as compared with children complete their vaccination. This is comparable with the study finding in Adama referral hospitals [17] and university of Gonder [19]. The finding of this research also indicated that HIV infected children having sever stunting was independently associated with incidence of TB as compared with HIV infected children has no stunting. This in line with the study finding in Adama [17],Tanzania[10], Uganda & Zimbabwe [11]. This might be due to HIV infection increases nutrient mal-absorption due to metabolic alterations that culminate in weight loss and stunting with time leads early exposed for opportunistic infections [29]. Similarly existence of 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 HIV infected children having hemoglobin level >10 mg/dl. This is in line with the study finding in Adama hospitals [17],university of Gonder referral hospitals [19] ,Northern Ethiopia[20], Dar es Salaam, Tanzania[10], in England and wales[23]. In fact this is due to hemoglobin levels had high predictive value for incident TB and death. TB incidence is directly associated with severe anemia [35]. Regardless of ART moderate or severe anemia during ART follow up 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

AHR: Adjusted Hazard Ratio, WFH: Weight for Height, WFA: Weight for Age, HFA: Height for Age, PYOs: Person Years of Observations, CI: confidence interval,

Declarations

Ethical approval

Ethical approval was first obtained from Ethical review Committee of College of medicine and Health Sciences department of public health in Debre Markos University. First formal letter was written from the university ethical board to Assosa and Pawe General Hospitals for data collection permission .After accepting and giving permission for collections of data by administrative staff in two general hospitals formal letter was written based on our request for work in ART paediatrics ward to conduct the study. Finally, individual consent from the study participants by their formal signature and a few of them by thumb finger to keep their confidentiality.

Consent for publications

No consent for publications

Availability of supporting data

All the datasets analyzed for this study is/are available in the corresponding author and can send based on reasonable request.

Competing interests

The authors declare that there are no competing interests.

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Author's contributions

FKB has developed designing study, training data collectors, supervising the data collectors

TSF has worked on data cleaning, editing, entering, result writing,

TTD has participated on result interpretation

BM has participated on manuscript writing.

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Tables

Table1: 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 N=421	Percent 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
	<=10mg/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
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

Table2-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%

Table3: Bivariable and multi variable cox-proportional hazard analysis for time to develop TB among children treated on ART OPD at Assosa and Pawe General Hospitals 2009-2018

Survival status of children				Multivariable cox regression			
ables		TB incidence	Censored	CHR 95% CI	P-value	AHR=95% CI	
of children	< =5	2	85	1			
s							
	6-10	12	134	3.4 (0.7	0.68	1.38	(0.28
s				15.52)		6.6)	
	>=11	50	138	12.(12.7	0.12	2.89	(0.62
s				49.6)		12.)	
azid	yes	15	243	1		1	
	No	49	114	6.58(3.6	0.80	0.91(0	.41
				11.7)		1.9)	
imoxazoles	yes	28	293	1		1	
	No	36	64	4.7(2.87	0.003	2.5	(1.4
				7.75)		4.74)*	
istory of contact	Yes	53	82	12.21(6.6	0.002	3.7	(2.89
				23.4)		7.2)*	
		11	275	1		1	
ination	status	23	253	1		1	
plete							
		33	43	5.75(3.4,	0.005	2.6(1.32	
ult				9.72)		4.5)*	
	Not	8	61	1.24(0.5,	0.25	1.68	(0.66
stered				2.87)		4.1)	
count	Above	28	280	1		1	
shold							
	Below	36	77	1.58(0.91	0.403	0.72(0.37	,
shold				2.74)		1.42)	
Adherence		21	223			1	
l							
		15	104	1.9(0..89	0.817	1.2(0.48	,
				4.07)		2.94)	
		28	30	7.1(0.37	0.746	1.19(0.52	
				26.32		2.71)	
ht for age	(HFA)	35	249	1		1	
nal							
		21	83	1.64(0.95	0.06	1.32(0.62	
lerate				2.82)		2.71	

	Sever	8	25	1.93(0.89 4.1)	0.03	2.96(1.2 7.88)*	
ing							
)	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)	
oglobin	>	10	251	1			1
il							
	< =10	52	106	9.62(5.13 18.0)	0.001	4.02 (2.1 8.1)*	
il							

Figures

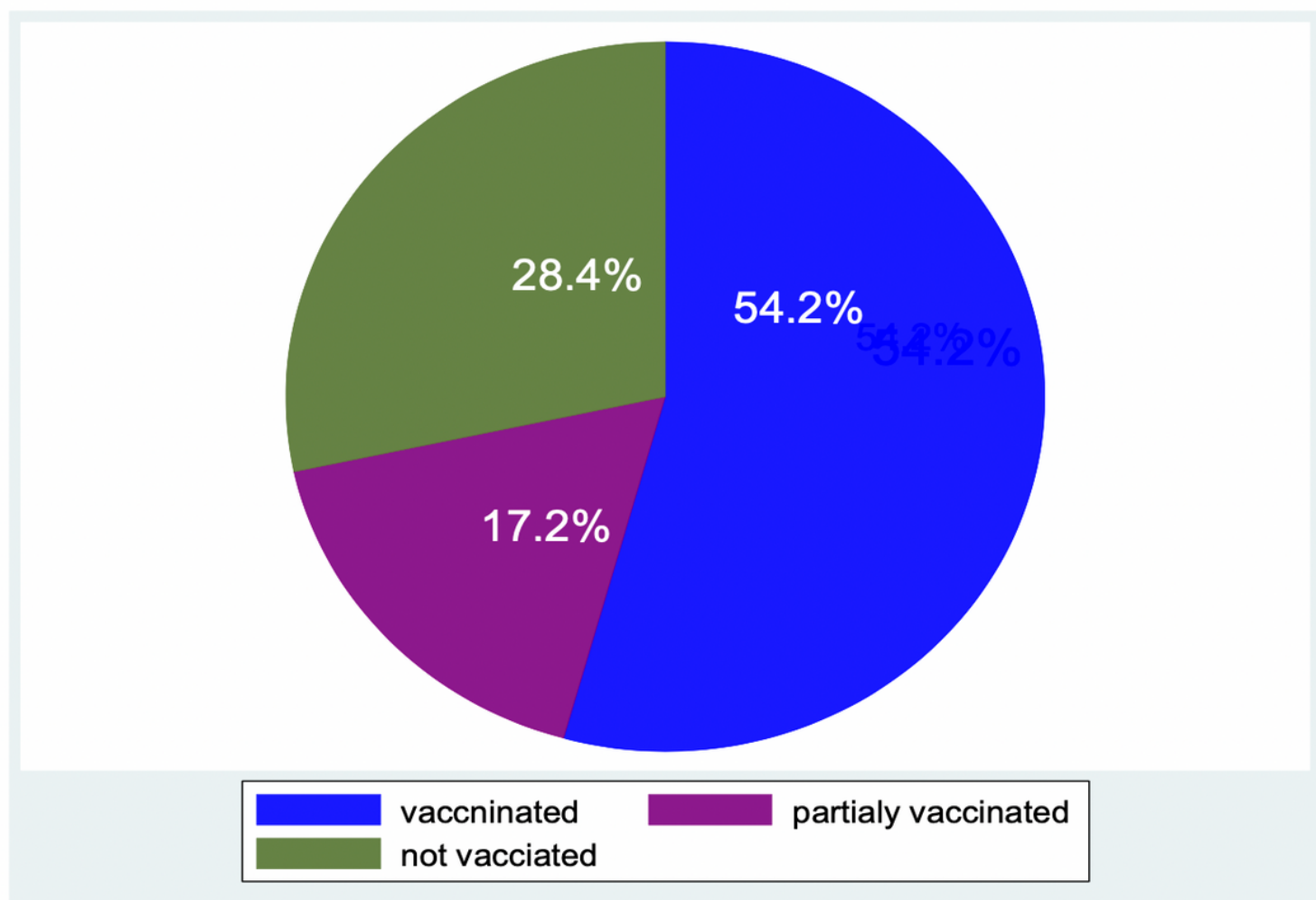


Figure 1

vaccination status of HIV infected children in Pawe General Hospital during ART follow up time since 2009-2018

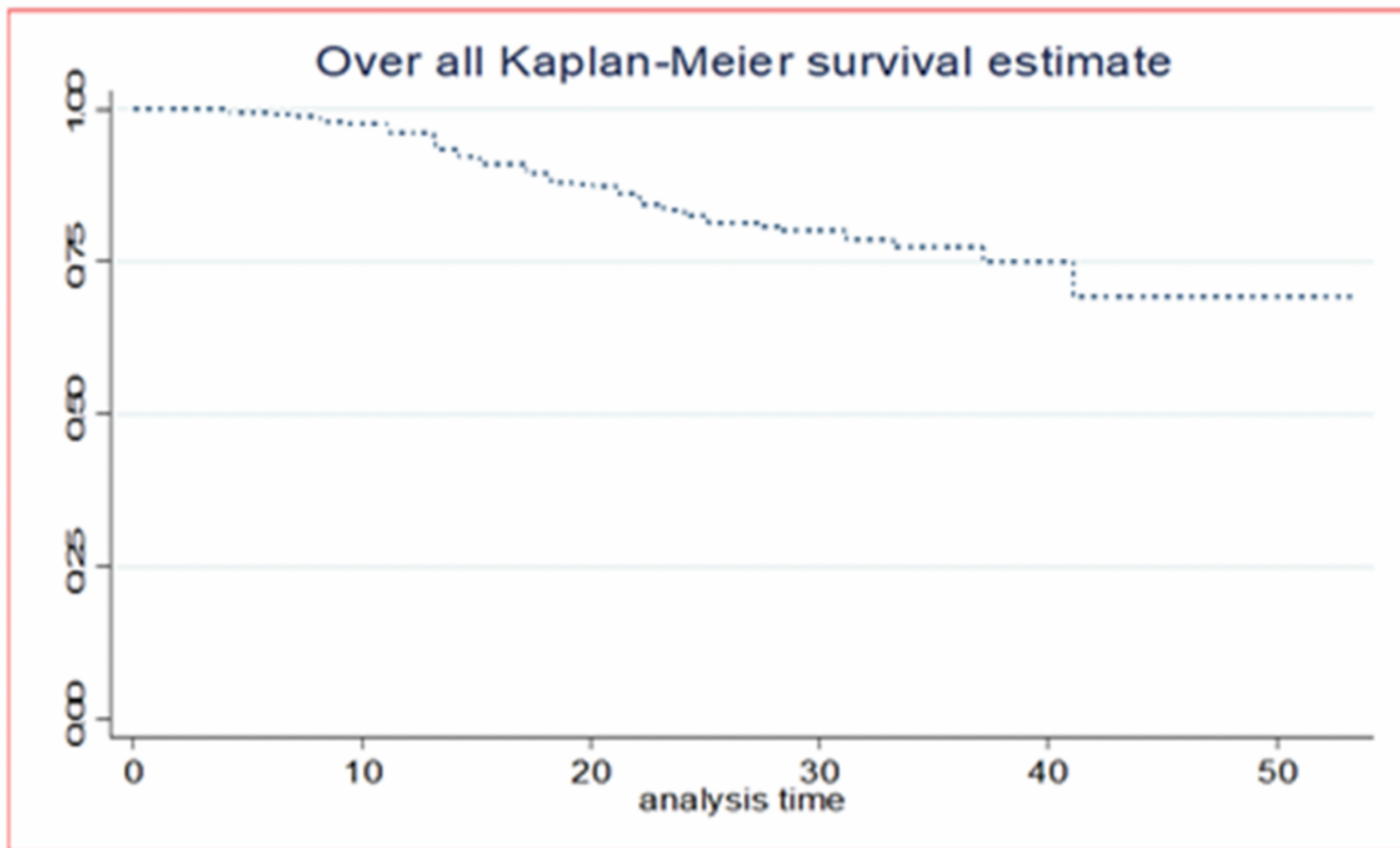


Figure 2

The overall Kaplan-Meier TB free survival probability of HIV infected children from tuberculosis incidence since 2009-2018.

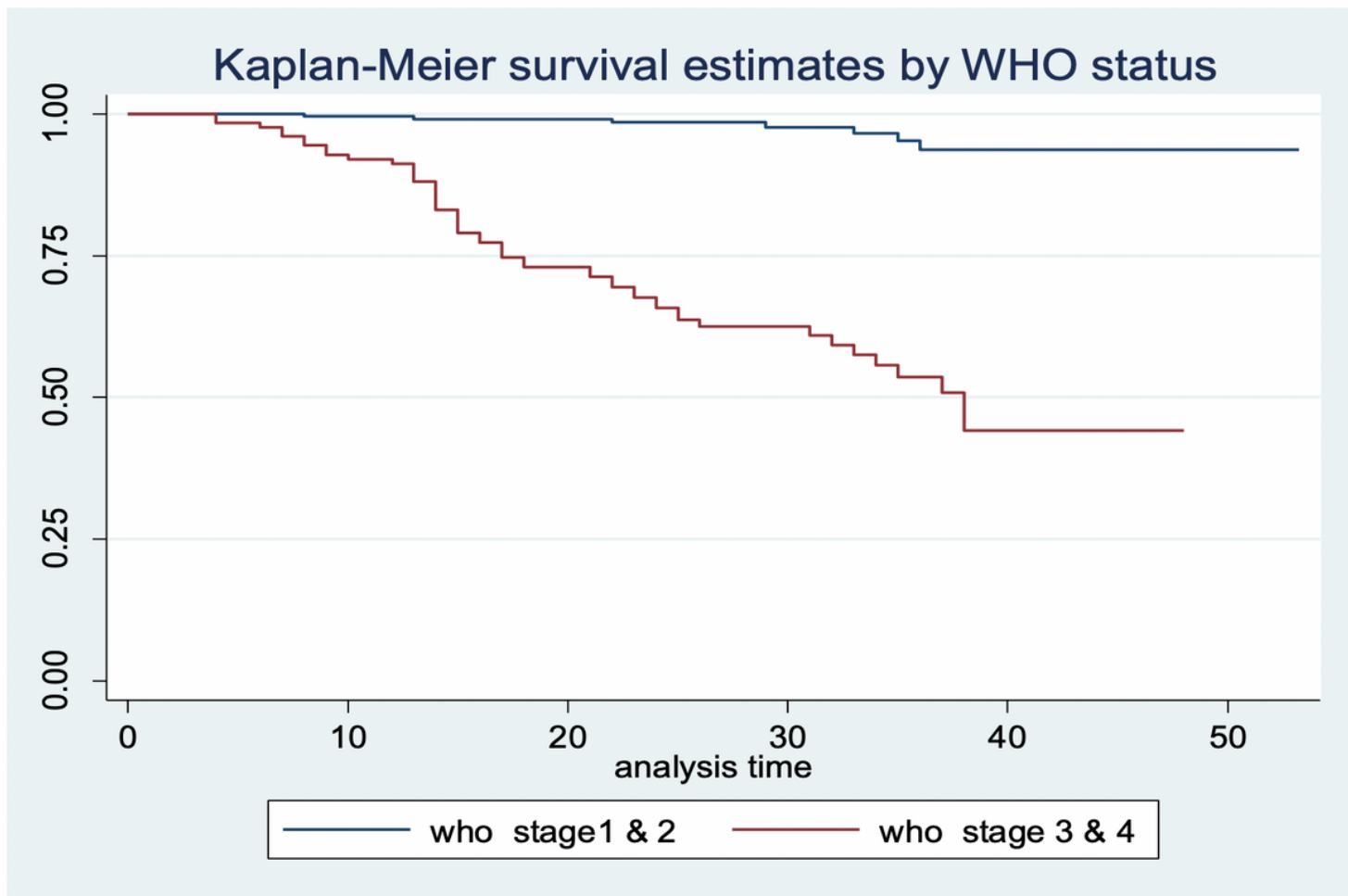


Figure 3

Kaplan Meier survival estimate based on who clinical stage stratification among HIV infected children at Assosa and Pawe general hospitals since (2009-2019.)

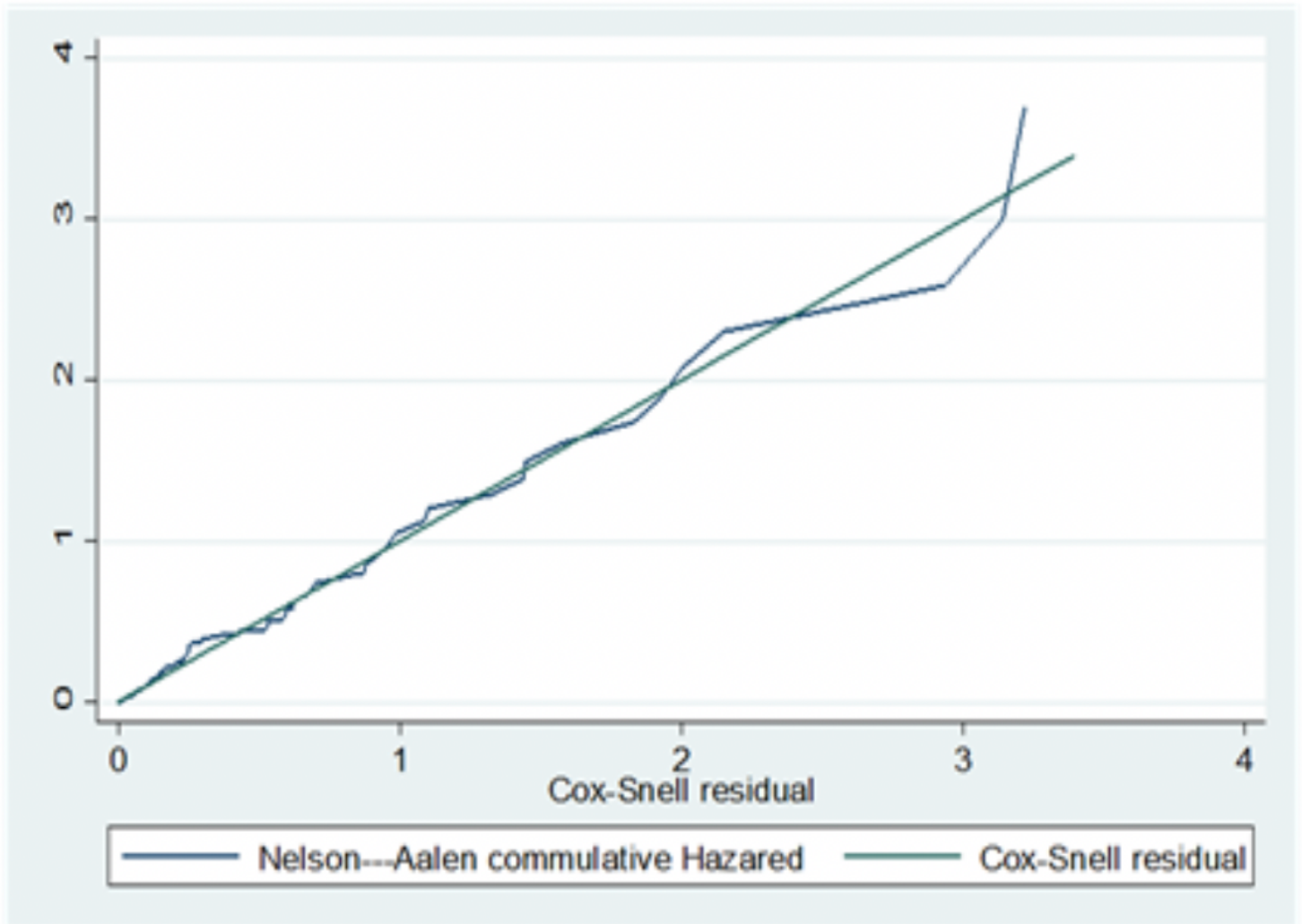


Figure 4

Model adequacy for time to develop TB among HIV infected children in Northwest Ethiopia based on by Nelson Aalen and Cox- Snell residual test.