**Research Article**
Volume 10:7, 2020

Journal of
Pulmonary & Respiratory Medicine

ISSN: 2161-105X

Open Access

# Time to Develop Pulmonary Tuberculosis and Predictors among HIV Infected Children Receiving Anti-Retroviral Therapy in Assosa and Pawe General Hospitals, North West Ethiopia: A Retrospective Cohort Study

**Fassikaw Kebede Bizuneh[1*], Dube Jara Boneya[2], Abebe Abate Dessie[3]**

*[1]Department of Epidemiology, Faculty of Public Health, Institute of Health Jimma University, Jimma, Ethiopia*

*[2]Department of Public Health, College of Health Sciences, Debre Markos University, Debre Markos, Ethiopia*

*[3]Department of Nursing, Collage of Health Science, Debre Markos University, Debre Markos, Ethiopia*

## Abstract

**Introduction:** Recently, pulmonary tuberculosis (PTB) incidence is a serious co-infection and an emerging global concern for children living with human immune deficiency virus (HIV). However, the incidence of PTB among adult HIV patients is exhaustively studied; the incidence of PTB among children on ART is overlooked. This research provide indispensible time-based relevant interventions clues.

**Objective:** Hospital-based retrospective cohort study was conducted among 359 HIV infected children, those registered on ART since 2009-2018. Time to develop PTB was defined as the time from enrollment for ART care until the development of PTB. Survival analysis was used and the proportional hazard assumption was checked for each variable and no variable was found with Schoenfield test <0.05. Variables with P-value <0.25 in bivariate Cox regression analysis were entered into the multivariable Cox model. Multivariable Cox regression model with 95% CI and AHR was used to identify the significant predictors.

**Materials and Methods:** We conducted facility based retrospective cohort study from January 1/2009 to December 31, 2018 at Assosa and Pawe general hospitals in Benishangule Gumuz region. Both hospitals are located in North West Ethiopia; this region is one of the regional states established in 1994 by the constitution of Ethiopia. It is located in the western part of Ethiopia between 34° 10'N and 37° 40'E; and in the latitude 09° 17'N and 12° 06' N. Assosa is the capital city of the region, it is located at a distance of 659 km in the west, and Pawe is located a distance from 565 km from in North West direction of Addis Ababa.

**Results:** This included individual records of 359 HIV-infected children initiated ART with in the period of January 1st 2009 to December 31 2018. During the follow-up period, totally 686.5 Persons per Year of observation (PYOs) were produced with minimum and maximum follow-up time on ART was 0.34 & 5.1 years, respectively. The overall incidence rate of PTB was found 2.78 (95% CI: 2.4-5.76) per 100 child-years of observation. Age group ≥ 11 years (AHR=5.1 95% CI: 1.4-18), advanced Who stage III&IV (AHR=3.4 95% CI: 1.2-9.7), Being severed underweight (AHR=3.2 95% CI: 1.3-7.8), Not started Isoniazid preventive therapy (INH) (AHR=2.8, 95% CI: 1.1-7.2) and having previous opportunistic infections (OIs) (AHR=2.34 95% CI: 1.3-4.1) were significantly associated with PTB occurrence.

**Conclusion:** The findings of this study indicated, the incidence rate of PTB among HIV infected children remains has high health impact. Concerning associated factors such as advanced who stage III& IV, being severe underweight, not started, isoniazid prophylaxis, and previous OIs is significantly associated with PTB incidenced.

**Keywords:** Time to develop • Predictors • HIV infected children • Pulmonary TB • Ethiopia

## Introduction

Pulmonary tuberculosis (TB) is one of the comrade causes of morbidity and mortality with in human immunodeficiency virus (HIV) for HIV-infected children [1]. Its dual co-infection with HIV for children less than 15 years is an emerging global concern [2,3]. Depletions of immunity by rapid viral reproduction increase the susceptibility for progressions of reactivations of latent mycobacterium to active TB infection [1]. Study results on HIV infected children indicated, the incidence of PTB as co-infection provokes sputum conversion period by remaining extensive cavitation lesion in the lung [4], this made delay on standard treatment outcome [2,5]. Currently, the incidence of pulmonary tuberculosis among HIV-infected children is high,in twines epidemic countries extends 830 -17,500/ 100- 000 P-Y [6]. Childhood TB is often called "the hidden epidemic" due to the difficulties involved in finding and treating the disease in this population [7]. A study result in 2015 among selected high TB burden and most populous countries revealed, death rate of tuberculosis in children accounted 239 000 -298 000 (15-20%) [7,8]. Globally in 2016, among newly diagnosed 235,000 HIV infected children, 7.20% seropositive children develop dual incidence of PTB [9], similarly in china the incidence rate of PTB range 2.26-4.92/100 P-Y [1]. Different study result among HIV infected children indicated, factors contribute for PTB occurrence during successive cohort

***Address for Correspondence:** Fassikaw Kebede Bizuneh, Department of Epidemiology, Faculty of Public health, institute of Health Jimma University, Jimma, Ethiopia, E-mail: easterkeb@gmail.com*



**Received** 29 October, 2020; **Accepted** 18 November, 2020; **Published** 25 November, 2020

follow up were identified, some of them, WHO clinical stage 3&4 [10], residence [2], not started isoniazid [11]. Sub-Saharan Africa countries accounts for the lion's share of TB incidence, TB–HIV co-infections, and TB–HIV deaths. One underlying reason is the relatively low coverage and quality of TB prevention, treatment, and care programs [3]. Ethiopia is among the 22 high burden TB countries and ranked fourth in Africa with top 17 TB-HIV twines epidemic site, More than 3900 seropositive children developed PTB [12,13]. Recently, pulmonary tuberculosis incidence was found an emerging global concern [14], in fact it is one of the leading lethal opportunistic infection for people living with HIV/AIDS [15-18]. Although, studies have been extensively conducted on pulmonary tuberculosis incidence on adult patient [19,20], however incidence of Pulmonary TB among children was incompletely described and overlooked [15,21]. Thus, this study assessed the incidence and predictors of PTB in two selected General hospitals in Northwest Ethiopia.

# Materials and Methods

## Study area, design and study population

We conducted facility based retrospective cohort study from January 1/2009 to December 31 /2018 at Assosa and Pawe general hospitals in Benishangule Gumuz region. Both hospitals are located in North West Ethiopia; this region is one of the regional states established in 1994 by the constitution of Ethiopia. It is located in the western part of Ethiopia between 34° 10'N and 37° 40'E; and in the latitude 09° 17'N and 12° 06' N. Assosa is the capital city of the region, it is located at a distance of 659 km in the west, and Pawe is located a distance from 565 km from in North West direction of Addis Ababa. This region has two general and three primary hospitals. This two general hospitals are routinely diagnosed and treat tuberculosis based on the clinical findings, the chest x-ray and AFB [22]. In both general hospitals there has been given ART care service by 2007 pediatric HIV/AIDS guideline updated in 2015 [23]. Following the time of enrollment to ART care continuum, all children have started ARV at both hospitals. Study population includes all HIV posetive children 216 and 185 were on follow up care started at Assosa and Pawe general hospitals, respectively. However, from the registration logbook, 42 card outcome variables were not registered and finally excluded.

## Source and study participants

The source populations for this study were all HIV infected children (aged < 15 years) with ever-initiated HIV/AIDS care at Pawe and Assosa general hospitals, with the study population including those HIV-infected children started on ART between January 1st, 2009 to December 31, 2018. HIV infected children who had incomplete baseline information (CD4 count, hemoglobin level, who stage, weight, and height) and/or who had not the time of ART initiation were excluded from the study. All HIV infected children aged less than 15 years who enrolled into chronic HIV care at Assosa and Pawe referral hospitals registered from January 1st 2009 to December 30, 2018 for care were study subjects.

## Study variables

In this study, the outcome variable was the time to develop pulmonary tuberculosis; cases were only those who developed new PTB during the follow-up period. The outcome variables ascertained if PTB occurred only after registering for HIV/AIDS care and during successive follow-up time.

## Independent variables included

Age of children, sex, residence, family size, 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).

## Sample size determination

Sample sizes for this study were calculated by using STATA/SE 14 using Mark Waver and Freedman principles of survival sample size calculation by proportional allocation of the two groups $\pi 1 = \pi 2$.

Sample size (n ) =Number of event / Probability of event [24]

1) Z a/2 significant level a/2 0.05 =1.96, Power ZB=0.8 AHR =2.23 [25]

2) Event = (Za/2 + ZB )2 =251 by substitution each parameter into formula

$\pi 1\ \pi 2$ (log AHR)2

P (event) =1- ($\pi 1$ S1 (t) + $\pi 2$S2 (t)) freedman principles [24]

H0: S1 (t) =S2 (t), for all t

3) P (event) =1-0.5 (0.5+0.21) =0.7, S1 (t) & S2 (t)

4) N =Event / P (event) =251/ 0.7 =359

In this case, totally in both Assosa and Pawe hospital there are 401-registered HIV infected children starting service care since 2009-2018. Therefore, we included this entire card and no sampling procedure is used.

## Operational definitions

**Case ascertainment:** The outcome variables was diagnosed based on bacteriological, molecular, histopathology and clinical methods by using (Microscope, Sputum culture, Chest x-ray or Combinations) during patient presentation for PTB symptoms [13].

**Pulmonary TB:** A type of TB in which involves only lung parts, diagnosis is based on Smear, Culture, Radiology suggestive and symptoms based on HIV positive patients [26].

**Smear negative Pulmonary TB:** At least three sputum specimens negative for AFB, and Radiologic abnormalities consistent with active tuberculosis, and the decision by a clinician to treat with a full course of Anti-TB chemotherapy, or A patient with AFB smear-negative for sputum, however culture-positive and diagnosed as smear negative Pulmonary tuberculosis [26].

**Smear positive pulmonary TB:** Is confirmed the bacteria at least 2 out of three AFB smear result positive and diagnosed as smear-positive Pulmonary TB [26].

**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 [1,27].

**TB history of contact:** Children during HIV/AIDS care follow-up before TB incidence developed having a history of surviving or contact at any time with who has active TB diagnosed patients.

**Seropositive:** Children<15 years were confirmed, diagnosed with HIV / AIDS, and under follow-up.

## Data collection tools and quality control

Four bachelor nurses and two supervisors were selected for data collection processes and all had taken ART training. For the quality of the data collection process, a one-day training was given in two hospitals with two supervisors for data collectors. The principal investigator and two supervisors followed data. Data were collected using the data abstraction tool and medical history sheet prepared from the Ethiopian Federal Ministry of health HIV/AIDS follow up forms [14].

## Data processing and analysis

Data were entered using Epi Data version 3.02 and analysis was done using STATA Version14 statistical software. Data were cleaned and edited before analysis. The data were described in terms of central tendency (median) and dispersion (IQR), in frequency distribution, and graphically for categorical data. Days were used as a time scale to calculate time to recovery. The outcome of each participant was dichotomized into censored event (recovered). In this study, an acute form of malnutrition was assessed among the participants using the Z-SCORE charts of weight for height or length. Z-scores of between -3SD and ≤ -2SD were equated to moderate acute malnutrition and Z-scores of ≤ -3SD were equated to severe acute malnutrition, also the presence of kwashiorkor was considered as severe acute malnutrition. The life table was used to estimate cumulative survival probabilities after admission. Kaplan

Meier survival curve and log-rank test were used to describe the survival function. Bivariable Cox-proportional hazard regression model was fitted for each predictor. Those variables having a p-value ≤0.25 in the bivariable analysis were selected. Then, the variable selection was undertaken using a stepwisebackward variable selection approach using a p-value ≤ 0.25 as a cut point. Cox proportional hazard assumption was checked for each covariate using Schoenfeld residuals tests, and graphically using a log-log plot of survival. Predictor drug regimen violates the proportional hazard assumption and the Cox-Snell residual suggested that the Cox proportional hazard model (Cox regression) does not fit the data adequately. Therefore, an extension of the Cox proportional hazard model was required for this data. Since predictors were tested as not time-dependent, the stratified Cox regression model was adequate to be used. To check the no-interaction assumption of the stratified Cox regression model, the likelihood ratio (LR) test was used by comparing log-likelihood statistics for the interaction and the noninteraction model. This LR test statistic had an approximately achi-square distribution under the null hypothesis that the noninteraction model was correct. The hazard ratio with its 95% confidence interval was used to measure the strength of association and the p-value < 0.05 was used to identify the statistically significant association. After multivariable cox regression was built by transforming from bi-variable P<0.25, for finally model selection, was selected by AIC & BIC criteria finally, the model adequacy was checked by Nelson Alana, and Cox Snell residual combination tests.

### Ethics statement

Ethical clearance was obtained from the ethical review committee of Debre Markos University, College of Health Sciences (Ref. No: HSC/984/16/18). 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.

## Results

### Baseline socio-demographic and clinical characteristics

A total of 401 HIV-infected children's medical records were retrieved. Of this, 42 were excluded from the analysis due to incompleteness of files. The remaining of 359 HIV infected children's card included on this study. The median age those infected children during HIV/AIDS diagnosed were 9years (IQR=3-14) Thirty eight percent of children were found between the age group of 6-10 years. There were slightly more girls than boys in this study female 152.92%) Vs. male responden 169 (47.08%). Slightly more than half of 51.0% of the study participants were lived in rural areas. Two hundred ten (58.50%) of the study participants had biological parents and lived together (Table 1).

### Baseline clinical, laboratory, and medication-related characteristics

From the total study participants, more than two-thirds of 78.27% of them addressed co-trimoxazoles prophylaxis during their successive cohort of follow.

**Table 1.** Baseline socio-demographic characteristics of children liv¬ing with HIV receiving ART in Assosa and Pawe General Hospitals for incidence and predictors of PTB 1/1/2009- 30/12/2018.

| Variables | Characteristics | Frequency | Percent |
|---|---|---|---|
| Sex | Male | 169 | 47.08 |
| | Female | 190 | 52.92 |
| Age | ≤ 5 years | 93 | 25.91 |
| | 6 -10 years | 137 | 38.16 |
| | ≥ 11 years | 129 | 35.93 |
| Residence | Urban | 183 | 50.97 |
| | Rural | 176 | 49.03 |
| Religion | orthodox | 156 | 43.45 |
| | Muslim | 74 | 20.61 |
| | protestant | 90 | 25.07 |
| | catholic | 31 | 8.64 |
| | others | 8 | 2.23 |
| Family size | ≤2 | 106 | 29.53 |
| | 3-4. | 191 | 53.2 |
| | 5-6. | 62 | 17.27 |
| Parental status | Both parent alive | 210 | 58.5 |
| | Paternal orphan | 100 | 27.86 |
| | Maternal orphan | 30 | 8.36 |
| | Both parent orphan | 19 | 5.57 |
| Mode of HIV diagnosed | Rapid | 279 | 77.72 |
| | PCR | 80 | 22.28 |
| Functional status | Working | 248 | 69.08 |
| | Ambulatory | 70 | 19.5 |
| | Bedridden | 41 | 11.42 |
| CPT | Yes | 281 | 78.27 |
| | Not | 78 | 21.73 |
| IPT | Yes | 214 | 59.61 |
| | No | 145 | 40.39 |
| Hemoglobin | <10 gram/dl | 126 | 35.1 |
| | ≥ 10 gram/dl | 233 | 64.9 |
| CD4 Count | < 100 | 14 | 3.9 |
| | 101-200 | 52 | 14.48 |
| | ≥ 200 | 293 | 81.62 |
| Who staging | Stage 1 | 102 | 28.42 |
| | Stage 2 | 129 | 35.93 |
| | Stage 3 | 81 | 22.56 |
| | Stage 4 | 47 | 13.09 |
| Vaccination status | Vaccinated | 195 | 54.32 |
| | Vaccination not updated | 62 | 17.27 |
| | Not recorded | 102 | 28.41 |
| Children status (during data collection time) | Being on follow up | 170 | 47.35 |
| | Lost from follow up | 25 | 6.96 |
| | Transfer in to adult cohort | 81 | 22.56 |
| | Transfer out | 55 | 15.32 |
| | Died | 8 | 2.23 |
| | Drop | 20 | 5.57 |
| Opportunistic infection | Yes | 103 | 28.69 |
| | No | 256 | 71.31 |
| ART Adherence | Good | 192 | 53.48 |
| | Fair | 104 | 28.97 |
| | Poor | 63 | 17.55 |
| Types of ART Regiment | 4c= AZT +3TC+ NVP | 231 | 61.84 |
| | 4d= AZT+3TC+EFV | 46 | 15.6 |
| | 1e= TDF+3TC+EFV | 59 | 16.16 |
| | 1a=d4T+3TC+NVP | 21 | 5.58 |
| | Others | 2 | 0.56 |
| ART regiment change | Yes | 74 | 20.61 |
| | No | 285 | 79.39 |
| Types of change | Shifting regimen | 53 | 71.62 |
| | Second regiment change | 21 | 28.38 |

However, 145 (40.39%) seropositive children remained not starting isoniazid after registering for HIV/AIDS care. Majority of 230 (64.07%) of the study participants were found WHO stage 1 and 2, and 126 (35.10%) HIV infected children developed anemia (Hgb≤10 gram/ml with a median of 11.5 (IQR =9.8-12.7) mg/dl. Nearly half of 47.35% of HIV infected children were found on the currently <15 age cohort follow up, 55 (15.32%) transferred out to other health institutions and 20 (5.57%) children's dropped their follow-up. Whereas two

percent of children reported as death, 54.32% of the total study participant of were fully vaccinated (Figure 1). More than half of 53.48%children had good ART drug adherence, on same way, 61.84% used first line pediatrics HAART regimen of 4c (AZT +3TC+ NVP) of children. However, 20.38% of the study participant shifted to second-line ART regimen.

## Baseline nutritional status

Regarding baseline nutritional status of HIV infected children categorized by age approximately a quarter of 26.7% were developed moderate underweight (WFA=-3-2 Z) whereas, 35 (9.47%) of participants showed wasting (WFA≤ -3 Z) and 25 (6.96%) (WFH≤ -3 Z) children developed stunting, respectively (Table 2).

## Survival status of HIV infected children

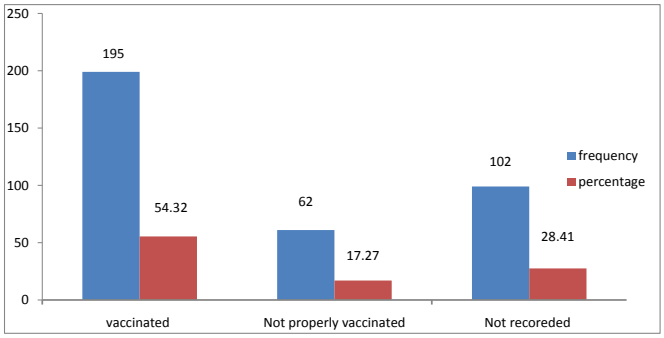


**Figure 1.** Vaccination status of HIV infected children lived in Assosa and Pawe general hospitals since 1/1/2009- 30/12/2018.

**Table 2.** Baseline nutritional status of HIV infected children registered for ART care in Pawe and Assosa general Hospitals 1/1/2009- 30/12/2018.

| S. No | Nutritional status | Numbers (%) |
|---|---|---|
| | **Baseline Nutritional status of children** | **Total children** |
| 1 | Normal weight for age (HFA ≥-2 Z) | 244 (67.9%) |
| | Moderate under (HFA between -3- -2 Z score) | 96 (26.7%) |
| | Sever underweight (HFA ≤ -3 Z score | 19 (5.29%) |
| 2 | Normal weight for Height (WFH ≥-2 Z) | 246 (68.52%) |
| | Moderate stunting (WFH between -3- -2 Z score) | 88 (24.51%) |
| | Severe stunting (WFH ≤-3 Z scores) | 25 (6.96%) |
| 3 | Normal weight for age (WFA ≥ -2 Z score) | 265 (73.82%) |
| | Moderate wasting (WFA between -3- -2 Z score) | 59 (16.71%) |
| | Sever wasting (WFA ≤ -3 Z score) | 35 (9.47%) |

More than two-thirds 83.57% of the study participant child observations were censored at the end of follow-up time. They produced 686.8 person years of observation; (PYO) risk time was obtained in censored followers. However during this time being children with advanced WHO clinical stage III and IV, having previous OIs, having sever underweight (≤ -3 Z score),and not started INH prophylaxis during HIV/AIDS care started time were less free survival and highly exposed for PTB incidence (Table 3).

## Pulmonary tuberculosis incidence rate

At the end of this follow, 686.5 person-years of observation (PYOs) were obtained with the minimum and maximum being 0.34 and 5.7 years of observations, respectively. Among all diagnosed PTB cases, 45 (76.27%) of the cases were Smear negative pulmonary TB and the remaining 14 (23.73%) of them were smear positive PTB events were diagnosed and treated (Figure 2). The cumulative incidence rate of PTB was found 58 (8.8%). The overall incidence rate was found 2.78 (95% CI: 2.4 -5.76) per 100 child-years of observations (Figures 3-5).

## Predictors of pulmonary tuberculosis

Being Age≥ 11 years, severe underweight, history of past OIs, advanced CLINICAL staging, hemoglobin ≤ 10 mg/dl, functional status,CD4 count, ART drug adherence status, isoniazid prophylaxis (INH) and ART initiation time were variables for multivariable analysis. Among this age≥ 11 years, having previous OIs, being advanced WHO clinical IIIℰIV, sever underweight and not taking INH prophylaxis were found significant predictors for pulmonary tuberculosis incidence. Children being age group ≥ 11 years were 5.1 times (AHR=5.1 95% CI: 1.4-18.) increase the risk of getting by pulmonary tuberculosis infection as compared with age group ≤5 years. Being who stage 3 & 4 (AHR =3.4 times more likely to develop PTB as compared with those children in WHO clinical stages I and II. This study also found that seropositive children being sever underweight (WFA≤- 3 Z score) nearly 3.2 times (AHR=3.2 95% CI: 1.3-7.8) more likely to develop PTB as compared with (WFA≥ -2z score). The risks of developing PTB among HIV infected children who did not start isoniazid prophylaxis therapy were 2.8 times (AHR =2.8, 95% CI: 1.2-7.2) more likely to develop PTB as compared with ever taking INH. the risks of developing

**Table 3.** Cumulative PBT free survival rate in HIV infected children at Assosa and Pawe general hospitals since1/1/2009- 30/12/2018.

| Years | Survival rate | 95% CI | New incidence | Cumulative | |
|---|---|---|---|---|---|
| 1 year | 96.40% | 0.93 ---0.98 | 12 | 12 | 20.3 |
| 2 years | 83.83% | 0.78---0.88 | 30 | 42 | 71.1 |
| 3 years | 77.56% | 0.62--- 0.84 | 6 | 48 | 82.1 |
| 4 years | 57.92% | 0.49-- 0.75 | 6 | 54 | 91.6 |
| ≥ 5 years | 39% | 0.37 ---55.5 | 5 | 59 | 100 |

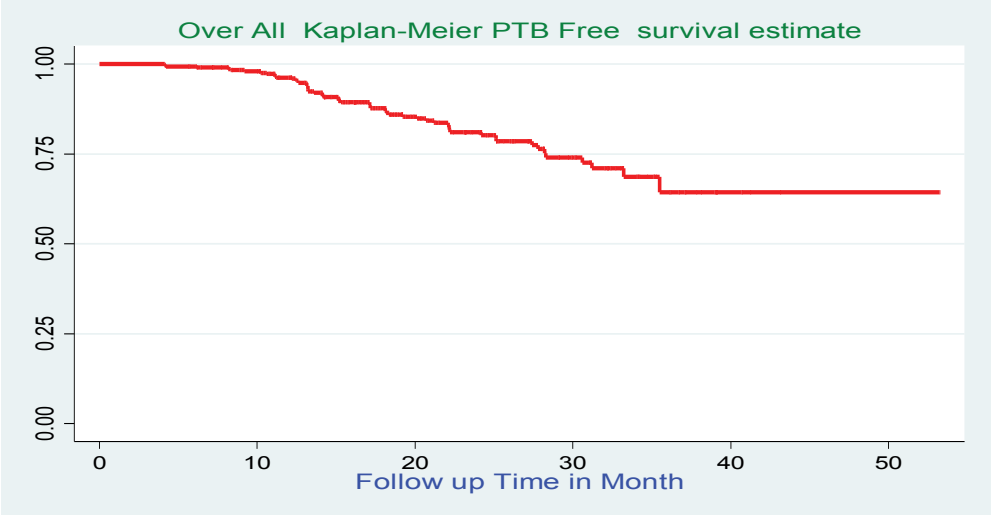


**Figure 2.** Over all Kaplan-Meier survival estimate for all HIV infected Children at Assosa and Pawe general hospitals from 1/1/2009- 30/12/2018.

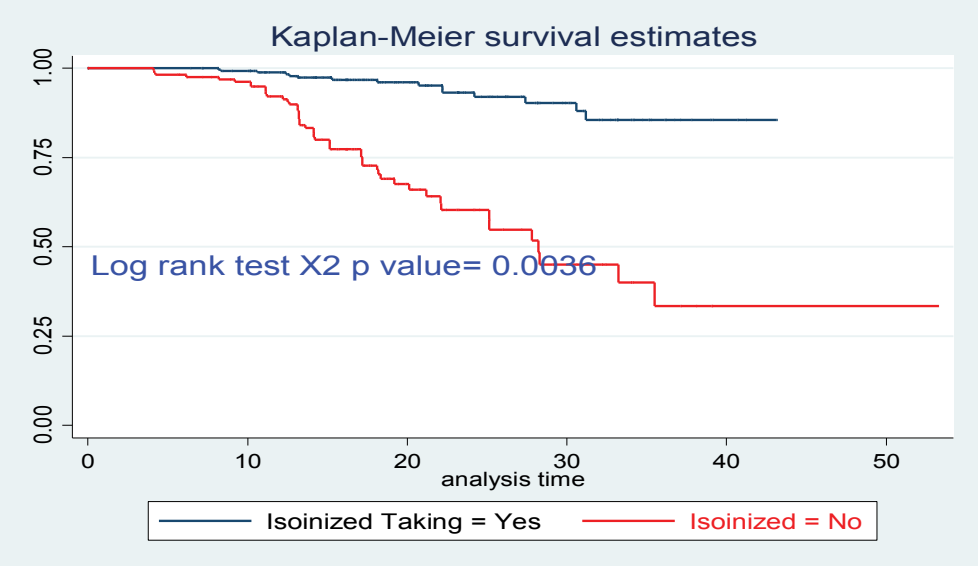


**Figure 3.** Kaplan-Meier survival estimate on Isoniazid, in HIV infected children at Assosa and Pawe general hospitals from 1/1/2009- 30/12/2018.

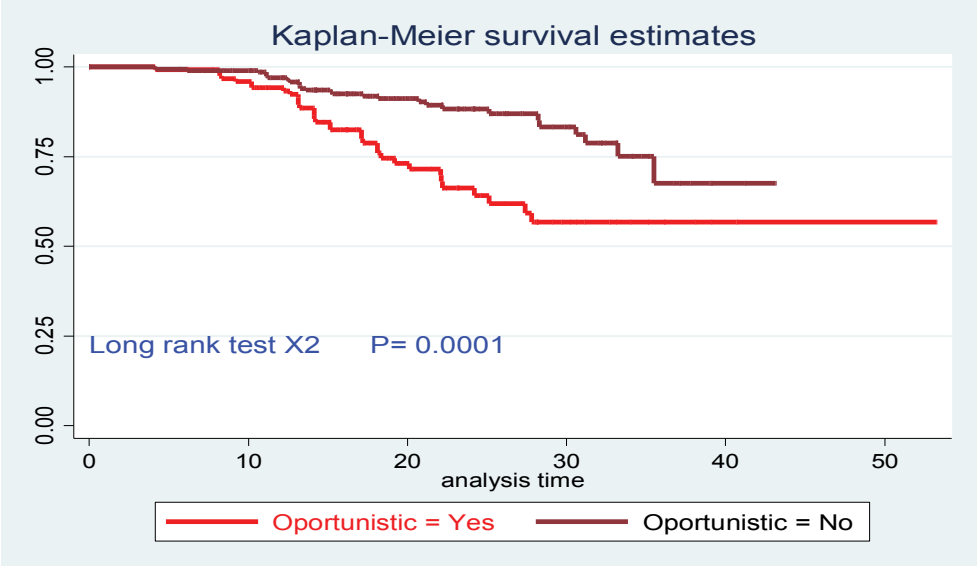


**Figure 4.** Kaplan-Meier survival estimate on previous opportunistic infection, in HIV infected children at Assosa and Pawe general hospitals from 1/1/2009- 30/12/2018.

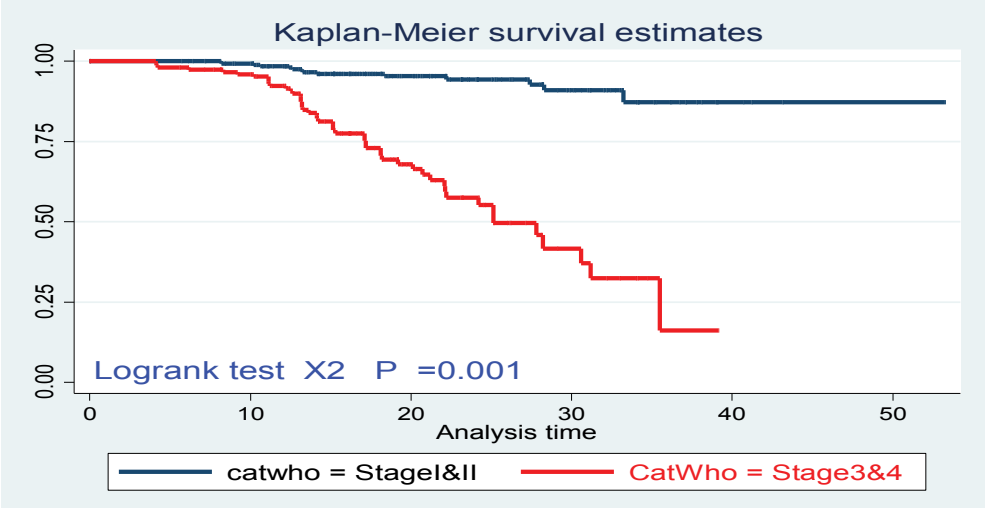


**Figure 5.** Kaplan-Meier survival estimate based on who stage in HIV infected children at Assosa and Pawe general hospitals from 1/1/2009- 30/12/2018.

**Table 4.** Bivariable and Multivariable cox proportional hazard regression model in HIV positive children at Assosa and Pawe General Hospitals, 1/1/2009- 30/12/2018.

| Variables | Survival status | | CHR | AHR | P. value |
|---|---|---|---|---|---|
| | Event | Censored | | | |
| **Age** | | | | | |
| ≤ 5 | 3 | 90 | 1 | 1 | |
| 06-10. | 32 | 105 | 7.5 (2.28, 24.38) | 3.18 (0.9, 11.1) | 0.07 |
| ≥ 11 | 24 | 105 | 5.98 (1.8, 19.86) | 5.08 (1.43, 18.0) | 0.012 * |
| **Hemoglobin** | | | | | |
| ≥ 10 gram/dl | 18 | 215 | 1 | 1 | |
| <10 gram/dl | 41 | 85 | 4.18 (2.76, 8.38) | 0.99 (0. 11, 1.18) | 0.144 |
| **ART initiation** | | | | | |
| Before 2013 | 20 | 133 | 1 | 1 | |
| After 2014 | 49 | 167 | 1.56 (0.91 2.68) | 1.3 (0.76 2.47) | 0.284 |
| **Previous OIs (Infections)** | | | | | |
| Yes | 34 | 69 | 3.74 (2.23, 6.279) | 2.34 (1.33, 4.1) | 0.003* |
| No | 25 | 231 | 1 | 1 | |
| **IPT** | | | | | |
| Yes | 6 | 208 | 1 | 1 | |
| No | 53 | 92 | 14.16 (6.1, 32.96) | 2.8 (1.099 7.19) | 0.031 * |
| **WHO staging** | | | | | |
| Stage 1 & 2 | 8 | 233 | 1 | 1 | |
| Stages 3 & 4 | 51 | 77 | 13.64 (6.5, 28.8) | 3.44 (1.21 9.74) | 0.020* |
| CD4 Count | | | | | |
| ≥ 200 | 38 | 255 | 1 | 1 | |
| 101–200 | 19 | 33 | 3.39 (1.95, 5.91) | 0 .73 (0.34, 1.71) | 0.227 |
| <100 | 2 | 12 | 1.14 (0.274, 4.72) | 0.35 (0.06, 1.9) | 0.355 |
| **WFA (Underweight)** | | | | | |
| Normal | 26 | 218 | 1 | 1 | |
| Moderate underweight | 24 | 72 | 2.5 (1.4, 4.34) | (0.6214, 2.36) | 0.574 |
| Sever underweight | 9 | 10 | 5.56 (2.61, 11.94) | 3.2 (1.32, 7.8) | 0.010* |
| **Functional status** | | | | | |
| Working | 17 | 231 | 1 | 1 | |
| Ambulatory | 20 | 50 | 4.3 (2.23, 8.15) | 1.62 (0.71, 3.7) | 0.248 |
| Bedridden | 22 | 19 | 2.84 (2.21, 5.6) | 0.95 (0.8, 1.16) | 0.87 |
| **Adherence** | | | | | |
| Good | 6 | 186 | 1 | | |
| Fair | 11 | 93 | 3.1 (1.3, 7.39) | 1.34 (0.41, 4.34) | 0.63 |
| Poor | 42 | 21 | 8.2 (4.64, 9.64) | 2.4 (0.85, 5.2) | 0.71 |

PTB among HIV infected children those developed previous opportunistic infection for HIV infected children were 2.34 times (AHR=2.34 95% CI: 1.3-4.1) more likely to develop PTB as compared with no developed any opportunistic infected during follow up times (Table 4).

## Discussion

This facility-based retrospective cohort study was undertaken to determine the time to develop pulmonary tuberculosis and predictors among HIV infected children receiving antiretroviral therapy in two general hospitals. From the total study participant, 16.45%of the study participants developed pulmonary TB during their follow up time, and yields the incidence rate of 2.78 Children/ 100 years (95% CI: 2.4-5.76). In fact, previous study finding showed in the study area of north west Ethiopia, has predominant distribution of PTB [22]. However, this finding is incomparable with study finding in china 0.8 per 100 child-years [6]. This can be due to study setting and time of ART initiation, unlike in China the study was conducted after all started ART. In fact, ART reduced 80-90% all endogenous reactivations of PTB incidence in the lungs [7,8]. From the finding of this study among predictors for PTB incidence, the risks of developing pulmonary TB among age ≥ 11 years were significantly associated with PTB incidence. This is in line with studies result in Cameron [10], TREAT Asia Pediatric HIV center (TApHOD) [28]. This is due to failure of immunity restoration due to chronic carrier [29]. Similarly, children highly experienced environmental & social interaction that easily acquired active PTB from chronic carrier patients [30]. The finding of this study indicated being WHO stage 3 and 4 in HIV infected children increases the risks of HIV infected children as compared with WHO stage 1 and 2. This is in line with the finding of china [1]. In advanced clinical stages due to immunity deterioration caused by repeated experience of infection which associated depletion of white blood cells & directly linked to a reduction in total lymphocyte count & CD4. All this predispose the incidence of pulmonary [30,31]. According to this study finding, being severely under nutrition (WFA≤ -3 Z score) was independently associated with the incidence of PTB. This finding was agreed with the study results in South Africa [32]. In HIV-infected children previous study results indicated, having poor oral intake leads mal-absorptions [33], Those brings final culminated wasting of body [34]. Similarly, the risks of developing PTB on having the previous history of opportunistic infection after started HIV care were significantly associated with PTB incidence. This result agreed with the study finding in South Africa [35] Nigeria [36]. In fact, on previous multicenter observational research finding indicated, incidence of infections other than

TB contribute 54-57 cells/mm3 substantially reduction of CD4 count [34]. This directly precipitate reactivation of Mycobacterium tuberculosis bacilli for active TB occurrence [37]. In this study, not received isoniazid (INH) was significantly associated with the incidence of pulmonary tuberculosis. This is in line with the study finding in Adama Hospital [8]. In fact, INH decreases mycobacterium load from endogenous reactivations of latent bacillus [6,37].

## Conclusion

The findings of this study indicated that Pulmonary TB remains a major public health problem for HIV infected children. Therefore, based on the above findings, we recommend consideration should be given to strengthening intensified screening isoniazid prophylaxis gaps and emergency therapeutics feeding is highly recommended for almost all HIV infected children. Furthermore, children presented with previous occurrence of OIs and advanced disease stage during ART initiation should be closely monitored and deeply investigated for the occurrence of PTB in each successive follow-up.

## Limitations of the Study

This study was a retrospective follow-up and depends on individual ART medical records, some exposure variable measurements varied with time and potential misclassification that arises from long study periods, PTB incidence might be underestimated due to excluded charts with incomplete data, variables, like income; not registered on the following form.

## Acknowledgment

I would like to thank Pawe and Assosa general hospitals, administrative staffs, and data collectors assisting during data collection.

## Data Availability

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

## References

1. Fang, Hews, Zhang, Furnis. "Incidence and associated factors of pulmonary tuberculosis in HIV-infected children after highly active antiretroviral therapy (HAART) in China: A retrospective study. " *AIDS care* (2014): 1127-1135.
2. Félicitée, Noel, Roger, Dewis. "Pulmonary Tuberculosis in Children with HIV Infection: From Symptoms to Diagnosis and Treatment in a Pediatric Center in Yaoundé-Cameroon. " *J HIV & Retro Vir* (2016): 6.
3. Genava. "WHO: Global TB report 2018" *WHO* (2018): 227.
4. Narendran, Gopalan, Soumya, Swaminathan. "Current trends of management of HIV-associated pulmonary tuberculosis. " *AIDS Res Ther* (2016): 34.
5. Andrew, Hesseling, Howells, Werschkull and Paul Donald. "Outcome of HIV infected children with culture confirmed tuberculosis." *Arch Dis Child* (2005): 4.
6. World Health Organization, Geneva . "WHO: Global TB Reports 2016" *WHO* (2016): 214.
7. Dodd, Paul, Courtne, Sismanidis and Charalambos, Seddon. "The global burden of tuberculosis mortality in children: A mathematical modelling study." *The Lancet Global Health* (2017): 898-906.
8. Masino,Tessu, Kenean, Getaneh and Tefera Mulugeta. "Incidence and predictors of tuberculosis among HIV-positive children at Adama Referral Hospital and Medical College, Oromia, Ethiopia: a retrospective follow-up study." *Epidemiology and Health* (2019): 41.
9. World Health Organization, Geneva . "WHO: Global TB Report 2017." *WHO* (2017): 147.
10. Luis, Abuogi, Mwachari Samuel. "Impact of expanded antiretroviral use on incidence and prevalence of tuberculosis in children with HIV in Kenya. " *Int J Tubercul Lung Dis* (2013): 112.
11. Auld, Arif, Shiraishi, Rao and Alfredo Christ. "Incidence and Determinants of Tuberculosis among Adults Initiating Antiretroviral Therapy - Mozambique,2004-2008. " PLOSE (2012): 54665.
12. "ETHIOPIAN National TB/HIV One Year Sentinel Surveillance." *EHNRI* (2013): 1-4.
13. "Guidelines for clinical and programmatic management of tb, leprosy and TB/HIV Ethiopia. " *FMOH* (2012).
14. "National guidelines for comprehensive HIV prevention, care and treatment. " *FMOH* (2014).
15. Yihun, Mulugeta, Ejigu, Gebeye. "High incidence of tuberculosis in the preventive therapy in children living with HIV in Northern Ethiopia: A retrospective follow-up study." *PLoS One* (2016): e0152941.
16. Akililu, Endalamaw, Eshetu, Hailesislasie. "Incidence of tuberculosis in children on antiretroviral therapy: a retrospective cohort study." *BMC Res Not* (2018): 11.
17. Atalell, Kia. "Survival and predictors of mortality among children co-infected with tuberculosis and human immunodeficiency virus at Universit. "*PLoS One* (2018): 13.
18. Sudjaritruk, Tim, Maleesatharn, Aish, Prasitsuebsai, Wells, Lumbiganon, Paul, et al. "Prevalence, characteristics, management, and outcome of pulmonary tuberculosis in HIV-infected children in the TREAT Asia pediatric HIV Observational Database (TApHOD)." *AIDS Patient Care STD* (2013): 649-651.
19. Ausman, Ahme, Atsede, Shiferaw and Fanuel, Belayneh. "Incidence and determinants of tuberculosis infection among adult patients with HIV attending HIV care in North-east Ethiopia: a retrospective cohort study." *BMJ* (2018): 1136.
20. Addis, Kris. "Incidence and predictors of tuberculosis among adult people living with human immunodeficiency virus at the University of Gondar Referral Hospital, Northwest Ethiopia." *BMC Inf Dis* (2013): 1-4.
21. Tavitiya, Sudjaritruk, Maleesatharn, Wasana and Prasitsuebsai, Siew. "Prevalence, Characteristics, Management, and Outcome of Pulmonary Tuberculosis in HIV-Infected Children inthe TREAT Asia Pediatric HIV Observational Database (TApHOD)." *Clinic Epidemol Res* (2013): 236.
22. Haimanot, Disassa, Adane, Worku. "A Preliminary Study on Molecular Characterization of Mycobacterium tuberculosis in Benishangul Gumuz Region, Western Ethiopia." *Bri Microbiol Res J* (2015): 223-227.
23. "Guidelines for Paediatric HIV/AIDS Care and Treatment in Ethiopia." *FMOH* (2007).
24. Mark, Ariel. Weaver, Peter. "Sample Size Calculations for single arm cohort in Survival Analysis". *BMJ* (2009): 212.
25. Sualiha, Gebeyaw, Akilew, Awoke. "Incidence and Predictors of Tuberculosis among HIV Positive Children at University of Gondar." *Hidawi* (2015): 307810.
26. "Ethiopian federal ministry of health: Tuberculosis, Leprosy and TB/HIV Prevention and Control Programme." *FMOH* (2008).
27. "WHO: World Health Organization child growth standards and the identification of severe acute malnutrition in infants and children." *WHO* (2006): 12.
28. Tavitiya, Sudjaritruk, Alan, Maleesatharn and Wasana, Prasitsuebsai. "Prevalence, characteristics, management, and outcome of pulmonary tuberculosis in HIV-infected children in the TREAT Asia pediatric HIV

Observational Database (TApHOD)." *Clinic Epidemiol Res* (2013): 12.

29. Anna, Turkova, Ali, Judd. "Prevalence, incidence, and associated risk factors of tuberculosis in children with HIV living in the UK and Ireland (CHIPS): A cohort study." *Lancet HIV* (2015): 221.
30. Kibret, Kim, Yalew, Watson and Belaineh, Gens. "Determinant factors associated with occurrence of tuberculosis among adult people living with HIV after antiretroviral treatment initiation in Addis Ababa, Ethiopia: A case control study." *PloS one* (2013): 64488.
31. Getachew, Tizazu, Tadesse, Anteneh. "Internal Medicine lecture note books." *PloS one* (2006): 556.
32. Aries, Hesseling, Homes, Werschkull and Paul Donald. "Outcome of HIV infected children with culture confirmed tuberculosis." *Arch Dis Child* (2005): 1171-1174.
33. "Ethiopian Federal Ministry of Health F: Guidelines for Paediatric HIV/AIDS Care and Treatment in Ethiopia." *FMOH* (2007).
34. "FMOH: National Guidelines for Comprehensive HIV prevention, care and treatment." *FMOH* (2017).
35. Hesseling, Amuel. "Outcome of HIV infected children with culture confirmed tuberculosis." *Arch Dis Child* (2005): 1171-1174.
36. Emmanuel, Anigilaje, Adekunle, Oris. "Tuberculosis, before and after Antiretroviral Therapy among HIV-Infected Children in Nigeria: What Are the Risk Factors?" PLos One (2016).
37. Mukuku, Omen, Mutombo, Morph and Kakisingi, Christ. "Tuberculosis and HIV co-infection in Congolese children: risk factors of death." *Pan African Med J* (2019): 326.

**How to cite this article:** Fassikaw Kebede Bizuneh, Dube Jara Boneya and Abebe Abate Dessie. "Time to Develop Pulmonary Tuberculosis and Predictors among HIV Infected Children Receiving Anti-Retroviral Therapy in Assosa and Pawe General Hospitals, North West Ethiopia: A Retrospective Cohort Study." *J Pulm Respir Med* 10 (2020): 519