Time to Develop Pulmonary Tuberculosis and Predictors Among HIV Infected Children Receiving Anti-Retroviral Therapy in Assosa and Pawe General Hospitals, North West Ethiopia 2020

Fassikaw kebede bizuneh (fassikaw123@gmail.com)
Institute of Health Jimma University
Dube Jara Boneya
Debre Markos University
Abebe Abate Dessie
Debre Markos University

Research

Keywords: incidence and predictors, HIV infected children, Pulmonary TB, Ethiopia

Posted Date: October 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-89428/v1

TIME TO DEVELOP PULMONARY TUBERCULOSIS AND PREDICTORES AMONG HIV INFECTED CHILDREN RECEIVING HIV CARE IN ASSOSA AND PAWE GENERAL HOSPITALS , NORTH WEST ETHIOPIA 2020

Fassikaw Kebede Bizuneh (BSc, MPH) [1*], Dube Jara Boneya (BSc, MPh, PhD fellow) [2], Abebe Abate Dessie (BSc, MSc) [3]

[1]Department of Epidemiology, Faculty of Public health, institute of Health Jimma University, Jimma Ethiopia. 2020

[2]Department of Public Health, College of Health Sciences, Debre Markos University, Debre Markos Ethiopia 2020

3Departement of Nursing, Collage of Health Science, Debre Markos University, Debre Markos Ethiopia 2020

AUTHORES EMAIL

FKB = fassikaw123@gmail.com
DJB = jaradube@gmail.com
AAD= abebeabate1@gmail.com

CORRESPONDING AUTHORE

Fassikaw Kebede Bizuneh ***fassikaw123@gmail.com***

Abstract: - 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 provides invaluable time based relevant actionsclues.

Objective:- Hospital-based retrospective cohort study was conducted among 359 HIV infected children those registered on ART since 2009-2018. Time to develop PTB defined as the time from enrollment for ART care until the development of PTB. The 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 the multivariable Cox model. Multivariable Cox regression model with 95%CI and AHR used to identify significant predictor.

Result:-Totally 359 HIV infected children followed and produced 686.5 Person per Years of observation (PYOs) with minimum and maximum follow up time on ART was 0.34 & 5.1 years, respectively. The median age of the children was 9 (SD±3.78) years. The overall incidence density of PTB was 7.2 Person/100years in 95%CI (5.52--- 9.24).Notably being age group >= 11 years (AHR=5.1 95% CI 1.4--18.), who stage 3&4 (AHR= 3.4 times increase the risks of PTB developed was compared WHO clinical stage 1& 2 (AHR=3.4 95%CI: 1.2-9.7). Being sever underweight (AHR=3.2 95%CI: 1.3--7.8), not started INHAHR =2.8, 95%CI: 1.1 -7.2) and having previous opportunistic infections (AHR= 2.34 95%CI: 1.3--4.1) significantly associated with PTB incidence.

Conclusion:-The incidence of PTB in HIV infected children were found higher as compared with evidence from previous findings. Strengthening intensified screening of INH and

therapeutic feeding needs for risk children highly recommended.

Keywords: incidence and predictors, HIV infected children, Pulmonary TB, Ethiopia

Introduction

Pulmonary tuberculosis (TB) is one of the comrade causes of morbidity and mortality with 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 a delay of standard treatment outcome[2, 5] .Currently, the incidence of pulmonary tuberculosis among HIV-infected children is high in twines TB-HIV epidemic countries 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 indicated tuberculosis death rate of children account 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]. In china the incidence range 2.26–4.92/100 P-Y [1]. . Different study result among HIV infected children indicated that factors contribute for PTB incidence were identified WHO clinical stage3&4[10],residence [2],not started isoniazid [11]. Global TB report of 2018 indicated ,Ethiopia found top 17 TB&HIV twine epidemic country [3]. The annual HIV cohort of pediatrics report each year in Ethiopia indicated, more than 3900 children develop incidence of PTB [12, 13].Recently pulmonary

tuberculosis incidence were found emerging issue[14]. Because of it is one of the leading lethal opportunistic infection [15-17]. Currently, Pulmonary tuberculosis incidence children is an emerging and global concern due to its one of leading lethal opportunistic infection for children living with HIV [18]. Although, studies have been conducted on pulmonary tuberculosis incidence on adult seropositive 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.

Methods

Study area, design and study population

We conducted a retrospective cohort study from January 1/2009 to December 31 /2018 at Assosa and Pawe general hospitals in Benishangule Gumuz. Both hospitals are located in Benishangule Gumuze regional state in North West Ethiopia. This region is one of the nine regional states in Ethiopia. Assosa is the capital city of the region, it is located at a distance of 659 km in west, and pawe 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, AFB and XpertTB for suspected TB patients[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 hospital. 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 cards outcome variables were not registered and were excluded.

Source and Study participants:

The source population for this study were all HIVinfected children (aged < 15 years) ever initiated on Pawe and Assosa general hospitals , with the study population including those HIV-infected children started on ART between January 1, 2009 to December 31, 2019. HIVinfected children who had incomplete baseline information (CD4 count, hemoglobin level, WHO clinical stage, weight and height) and/or who had OIs at the time of ART initiation were excluded from the study

Study variables

In this study, the outcome variable was Incidence of PTB. Incident PTB cases were only those who developed new PTB during the follow-up period. The outcome variables ascertained if PTB 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**).**

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

Sample size determination

Sample size for this study were calculated by using STATA/SE 14 using Mark waver and freedman principles of survival sample size calculations by proportional allocation $\pi 1 = \pi 2$

A) Sample size (n) = $\frac{\text{Number of event -[24]}}{\text{Probability of event}}$

1) $Z\ a/_2$ significant level a/2 0.05 =1.96, Power ZB= 0.8 AHR = 2.23 **[25]**
2) For incomplete data =10%
3) Event = $\frac{(Z_{a/2} + Z_B)^2}{\pi 1\ \pi 2\ (\log AHR)^2}$ = 251 by substitution each parameter into formula

P (event) = 1- (π1 S1 (t) + π2S2 (t)) freedman principles [24]

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

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

5) $\mathbf{N} = \frac{\text{Event}}{\text{P (event)}} = \frac{251}{0.7} = 359$

In case, totally in both Assosa and Pawe hospital there are 401 registered HIV infected children started for ART follow up since 2009-2018. Therefore, we included all this cards and no sampling procedures

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, and Xpert 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 ART follow up before TB incidence developed, having a history of survives or contact at any time with who has active TB patient.

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 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 the log-rank test was done. Hazard ratio with 95%CI & $P \leq 0.05$ was used to measure associated with the independent variable. The overall survival graph and hazard failure estimated curve was used to show survival and the hazard probability of the risk group. Cox-regression model was fitted to identify predictors for the incidence of pulmonary tuberculosis. All

predictors that were associated with the outcome variables in the bivariable analysis at a hazard ratio of P-value 0.25 or lower was included in the multivariable 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 Vs. graph test for each variable with the 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 finally, the of model adequacy was checked by Nelson Alana, and Cox Snell residual combination tests.

Result

Baseline socio demographic and clinical characteristics

From the total, four hindered one-study participants, 359(90.0%) study individual cards were included for final analysis. The median age those infected children during HIV/AIDS diagnosed were 9(SD±3.78) year. 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 190 (52.92%) Vs. male respondent 169(47.08%) with this slightly half of study participant (50.9%) was lived in rural area. Two hundred ten (58.50%) of the study participants has both parents and lived together. More than two-third 78.27% of the study participant addressed cotrimoxazoles prophylaxis during follow up time, however 145(40.39%) participants remain not started isoniazid. Majority of 230 (64.07%) of the study participant were found WHO stage 1&2 [Table1].

Among the total study participants, 126(35.10 %) HIV infected children has hemoglobin ≤10 gram/ml. From the total 359 study participants, 170 (47.35 %) were found < 15 years of cohort follow up, 55 (15.32 %) transfer out into other health institution .From this study finding,

210(58.05%) HIV infected children were lived with parents, from the total, study participant 195(54.32%) HIV infected children were vaccinated [Figure1]

Baseline Nutritional status

Among the total 359 children, 246 (68.52%) children is found in normal HFA≥-2 Z score but 35(9.47%) HIV infected children developed severs wasting (WFH≤-3 Z scores) & 96 (26.74%) HIV infected Children found in moderate wasting between (WFA= -3- -2 Z score).

Survival status of HIV infected children

Three hundred of the study participants (83.57 %) of the total HIV infected children observations was censored at the end of follow up times. During this times 609.2 PYO risk time was obtained in censored followers [Table2].

Pulmonary Tuberculosis incidence rate

At the end of this follow 686.5 person years of observation (PYOs) obtained with minimum and maximum is 0.34 and 5.7 years of observations found respectively. Among all diagnosed PTB case, 45(76.27%) of the case is Smear negative pulmonary TB and the remaining 14 (23.73%) of them were smear positive PTB events were diagnosed and treated [Figure2].The cumulative incidence rate of PTB was found 58(8.8%). The overall incidence density was found 7.2 Person/100years in 95%CI (5.52--- 9.24) [Figure 3-7].

Predictors of Pulmonary tuberculosis

During bivariable analysis, 15 variables were selected in the first steps of model building and 9 variables selected, as the best model by comparing AIC and BIC and 5 variables were found independently associated with predictors of PTB. Notably 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. In HIV infected children being who stage 3&4 (AHR= 3.4 times increase the risks of PTB developed was compared WHO clinical stage 1& 2(AHR=3.4 95%CI: 1.2-9.7). Being sever underweight HIV infected children were 3.2 times (AHR=3.2 95%CI: 1.3--7.8) increase the risk to developing PTB infections as compared with normal (WFA>= -2z score) not started INH were 2.8 times (AHR =2.8, 95%CI; 1.1 -7.2) increase the risks of PTB infections as compared with ever taking INH. Having previous opportunistic infection for HIV infected children were 2.34 times increased risks of PTB as compared with no previous opportunistic infections (AHR= 2.34 95%CI: 1.3--4.1)

[Table3].

Discussion

The finding of this study indicated that the incidence rate of Pulmonary TB was found 7.1 Children/ 100 years (95% CI: 5.5 --9.3). In fact previous study finding showed that in western part of Ethiopia has predominant distribution of PTB [22]. Also a study finding in china indicated that the incidence rate of PTB were found 0.8 children/100 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 in HIV infected age group belong to ≥ 11 years significantly associated. This agreed 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&4 in HIV infected children increases the risks of HIV infected children as compared with WHO stage 1&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 depletions of white blood cell & 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 result indicated, infections other than TB contribute in one round infection 54–57 cells/mm3 substantially reduction of CD4 count [34]. Which directly favors reactivation of Mycobacterium tuberculosis bacilli to change active TB infections [21, 34, 37]. In this study, not started 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]

Conclusions

The finding of this study indicated that Pulmonary TB remains major public health problem especially for HIV infected children. The finding of this study indicated being age group >= 11 years ,being Who clinical stage 3&4, being Sever underweight ,not started Isoniazid preventive therapy and having previous opportunistic infection were independent associated with PTB incidence. Strengthening intensified screening of INH for all HIV infected children and emergency therapeutics feeding is highly recommended for all HIV infected children

Limitations of the study

This study was 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, family education status; viral loads not registered on HIV infected children ART follow form.

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; AHR: adjusted hazard ratio; ART: highly active antiretroviral therapy; CD4: Cluster of Differentiation 4; CI: confidence interval; CPT: cotrimoxazoles prophylactic therapy; IPT isoniazid prophylaxis therapy, PTB pulmonary tuberculosis HIV: human immunodeficiency virus; prophylactic therapy; OI: opportunistic infection; WHO world health organization, WFA= weight for age, HFA =height for age, WFH= weight for height.

Funding
Not applicable

Acknowledgment

I would like to thanks 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.

Computing interest

The author declared there is no computing interest for this research.

Ethical approval

Ethical clearance was obtained from Review Ethics Committee of College of Health Sciences, Debre Markos University. First formal letter was written from Debremarkos University to Assosa and Pawe General Hospitals .After accepting and giving permitting for collections of data by administrative staff write formal letter for us, then we address for ART peadtrics ward to conduct the study. Moreover, consent to participate was not applicable since it is record review and patient confidentiality was kept while the study was conducted through review of medical records.

Consent for publication

No consent for publications

Competing interests

The authors declare that they have no competing interests.

Reference

1. Mu W, Zhao Y, Sun X, Ma Y, Yu L, Liu X, Zhao D, Dou Z, Fang H, Zhang F: **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, **26**(9):1127-1135.
2. Félicitée N NN, Roger D,et al: **Pulmonary Tuberculosis in Children with HIV Infection: From Symptoms to Diagnosis and Treatment in a Pediatric Center in Yaoundé-Cameroon**. *Journal of HIV & Retro Virus I* 2016, **Vol. 2 No. 1: 6**(DOI: 10.21767/2471-9676.100011):7.

3. WHO: **Global TB report, WHO genava 2018**. 2018:227.

4. Narendran Gopalan PC, Soumya Swaminathan: **Current trends of management of HIV-associated pulmonary tuberculosis**. *AIDS research and therapy* 2016, **13**:34.

5. A C Hesseling AEW, H Werschkull, P R Donald, N Beyers, G D Hussey,, W El-Sadr HSS: **Outcome of HIV infected children with culture confirmed tuberculosis**. *Arch Dis Child 2005* 2005, **doi: 10.1136/adc.2004.070466**:4.

6. WHO: **GLOBAL TB REPORTS WHO Geneva 2016** *Reports* 2016, **214**.

7. Dodd PJY, Courtney M.Sismanidis, Charalambos, Seddon JA: **The global burden of tuberculosis mortality in children: a mathematical modelling study**. *The Lancet Global Health* 2017, **5**(9):e898-e906.

8. MasinoTessuBeshir AHB, Kenean Getaneh Tlaye , Tefera Mulugeta Demelew: **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**(https://doi.org/10.4178/epih.e2019028):8.

9. WHO: **GLOBAL TB REPORT ,WHO Geneva 2017**. 2017:147.

10. L.Abuogi C. Mwachari LBS: **Impact of expanded antiretroviral use on incidence and prevalence of tuberculosis in children with HIV in Kenya**. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2013.

11. Auld AF MF, Shiraishi RW, Alfredo C, Sanchez M, et al.: **Incidence and Determinants of Tuberculosis amongAdults Initiating Antiretroviral Therapy – Mozambique, 2004–2008**. *PLOSE* 2012; P, **Volume 8 | Issue 1 | e54665**(Accesed online 1 22, 2013):11.

12. EHNRI: **ETHIOPIAN National TB/HIV ONE YEAR Sentinel Surveillance (July 2011 - June 2012)**. *Reports* 2013, **.www.ennonline.net**.

13. FMOH: **GUIDELINES FOR CLINICAL AND PROGRAMMATIC MANAGEMENT OF TB, LEPROSY AND TB/HIV IN ETHIOPIA**. *guideline* 2012.

14. FMOH: **NATIONAL GUIDELINES FOR COMPREHENSIVE HIV PREVENTION, CARE AND TREATMENT**. *Manual* 2014 **https://aidsfree.usaid.gov/sites/default/files/ethiopia_natl_gl_2014.pdf**:145.

15. Yihun Mulugeta Alemu GA, 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 11(4)* 2016, **PLoS ONE 11(4):e0152941**(DOI:10.1371/journal.pone.0152941):10.

16. Akililu Endalamaw, Eshetu Hailesislasie et.al : **Incidence of tuberculosis in children on antiretroviral therapy: a retrospective cohort study**. *BMC research notes* 2018, **11**:https://doi.org/10.1186/s13104-13018-13846.

17. Atalell KA: **Survival and predictors of mortality among children co-infected with tuberculosis and human immunodeficiency virus at Universit**. *plose* ne. 2018; 13.

18. Sudjaritruk T, Maleesatharn A, Prasitsuebsai W, Lumbiganon P, Kumarasamy N, Kurniati: **Prevalence, characteristics, management, and outcome of pulmonary tuberculosis in HIV-infected children in the TREAT Asia pediatric HIV Observational Database (TApHOD)**. *AIDS patient care and STDs* 2013, **27**(12):649-656.

19. Ausman Ahmed DM, Atsede M Shiferaw, Fanuel Belayneh,, Yenit MK: **Incidence and determinants of tuberculosis infection among adult patients with HIV attending**

HIV care in north-east Ethiopia: a retrospective cohort study. *BMJ* 2018 **V.8:e**(doi:10.1136/).

20. AddisK NaBWT: **Incidence and predictors of tuberculosis amongadult people living with human immunodeficiency virus at the University of Gondar Referral Hospital,Northwest Ethiopia**. *BMC Infectious Diseases 2013, 1* 2013, **http://www.biomedcentral.com/1471-2334/13/292**.

21. Tavitiya Sudjaritruk Alan Maleesatharn Wasana Prasitsuebsai, Siew Moy Fong NOL: **Prevalence, Characteristics, Management, and Outcome of Pulmonary Tuberculosis in HIV-Infected Children inthe TREAT Asia Pediatric HIV ObservationalDatabase (TApHOD)**. *CLINICAL AND EPIDEMIOLOGIC RESEARCH* 2013, **Volume 27, Number 12,** (DOI: 10.1089/apc.2013.0236).

22. Haimanot Disassa KTT, Adane Worku,: **A Preliminary Study on Molecular Characterization of Mycobacterium tuberculosis in Benishangul Gumuz Region, Western Ethiopia**. *British Microbiology Research Journal* 2015.

23. FMOH **Guidelines for Paediatric HIV/AIDS Care and Treatment in Ethiopia**. *Guidelines* 2007, **https://apps.who.int/medicinedocs/en/m/abstract/Js19145en/**.

24. Mark A. Weaver P: **Sample Size Calculations for single arm cohort in Survival Analysis**. *book* 2009.

25. Sualiha Gebeyaw , and KA, Akilew Awoke **Incidence and Predictors of Tuberculosis among HIV Positive Children at University of Gondar** *HIDAWI* 2015, **2015**:307810.

26. Ethiopian federal ministry of health F, ,: **Tuberculosis, Leprosy and TB/HIV Prevention and Control Programme**. *manual* 2008.

27. WHO: **World health organizations child growth standards and the identification of severeacute malnutrition in infants and children**. *SAM Manual* 2006:12.

28. Tavitiya Sudjaritruk M, ScM,1,2 Alan Maleesatharn, MBA,3 Wasana Prasitsuebsai, MD, MPH,: **Prevalence, characteristics, management, and outcome of pulmonary tuberculosis in HIV-infected children in the TREAT Asia pediatric HIV Observational Database (TApHOD)**. *CLINICAL AND EPIDEMIOLOGIC RESEARCH* 2013, **Volume 27, Number 12, 2013**.

29. Anna Turkova EC, Ali Judd, : **Prevalence, incidence, and associated risk factors of tuberculosis in children with HIV living in the UK and Ireland (CHIPS): a cohort study**. *The Lancet HIV* 2015,

30. Kibret KT, Yalew AW, Belaineh BG, Asres MM: **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, **8**(5):e64488.

31. Getachew Tizazu MD, Tadesse Anteneh MD: **Internal Medicine lecture note** *books* 2006, **1**:556.

32. A C Hesseling AEW, H Werschkull, P R Donald,: **Outcome of HIV infected children with culture confirmed tuberculosis**. *Archives of disease in childhood* 2005, **90**(11):1171-1174.

33. Ethiopian Federal Ministry of health F: **Guidelines for Paediatric HIV/AIDS Care and Treatment in Ethiopia**. 2007.

34. FMOH: **National Guidelines for Comprehensive HIV prevention, care and treatment**. *GUIDELINE* 2017.

35. Hesseling AC: **Outcome of HIV infected children with culture confirmed tuberculosis**. *Archives of Disease in Childhood* 2005, **90**(11):1171-1174.

36. Emmanuel A. Anígilájé SAA, Adekunle O. Adeoti3‡, Nnamdi, Nweke1 O: **Tuberculosis, before and after Antiretroviral Therapy among HIV-Infected Children inNigeria: What Are the Risk Factors?** *PLOSE* 2016.

37. Mukuku O, Mutombo AM, Kakisingi CN, Musung JM, Wembonyama SO, Luboya ON: **Tuberculosis and HIV co-infection in Congolese children: risk factors of death**. *The Pan African medical journal* 2019, **33**:326.

Figures

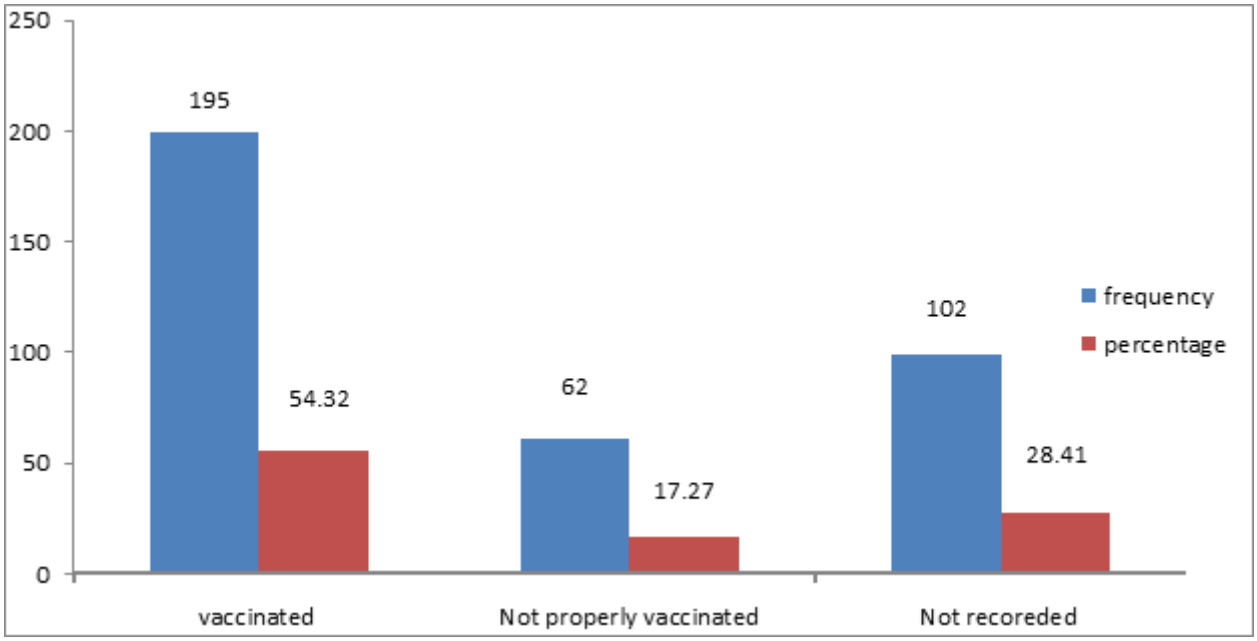

Figure 1

Vaccination status of HIV infected children lived in Assosa and Pawe general hospitals since 2009-2018

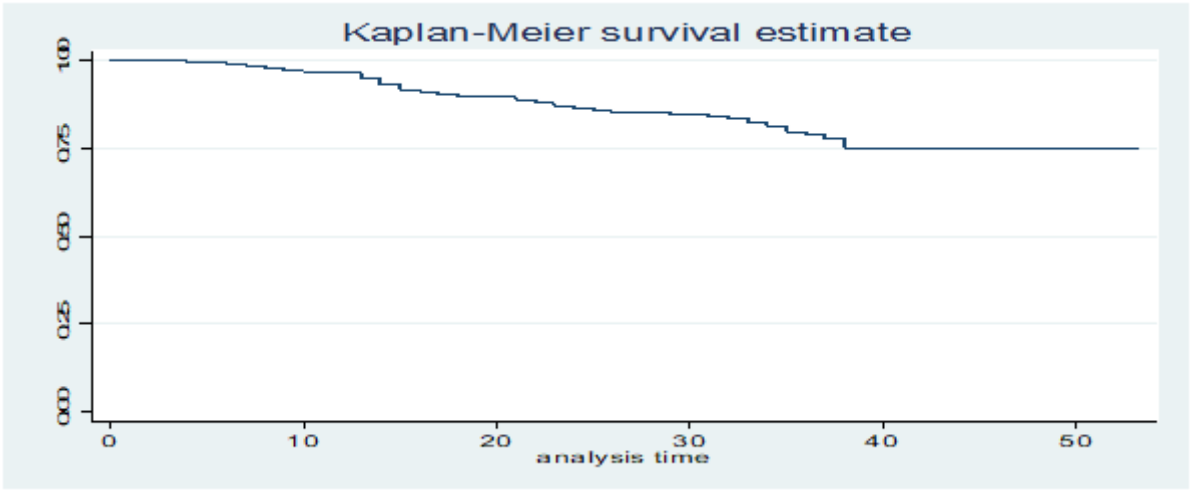

Figure 2

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

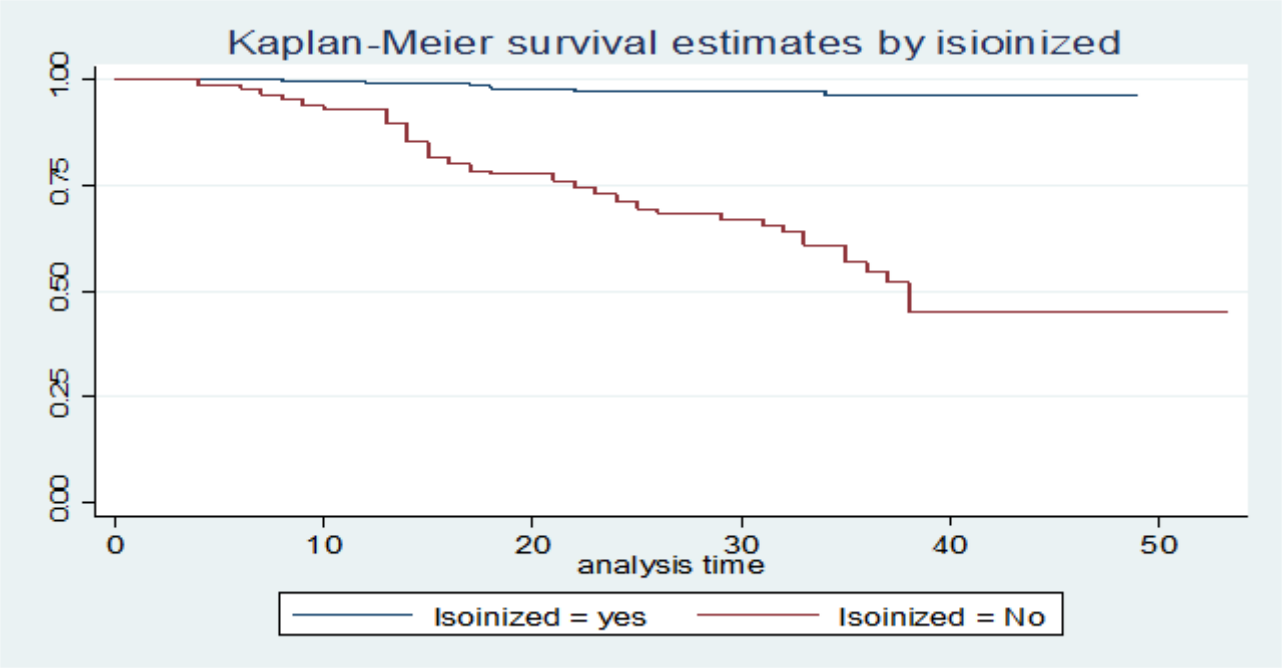

Figure 3

Kaplan Meier survival estimate on Isoniazid, in HIV infected children at Assosa and Pawe general hospitals from (1/1/2009- 30/12/2019)

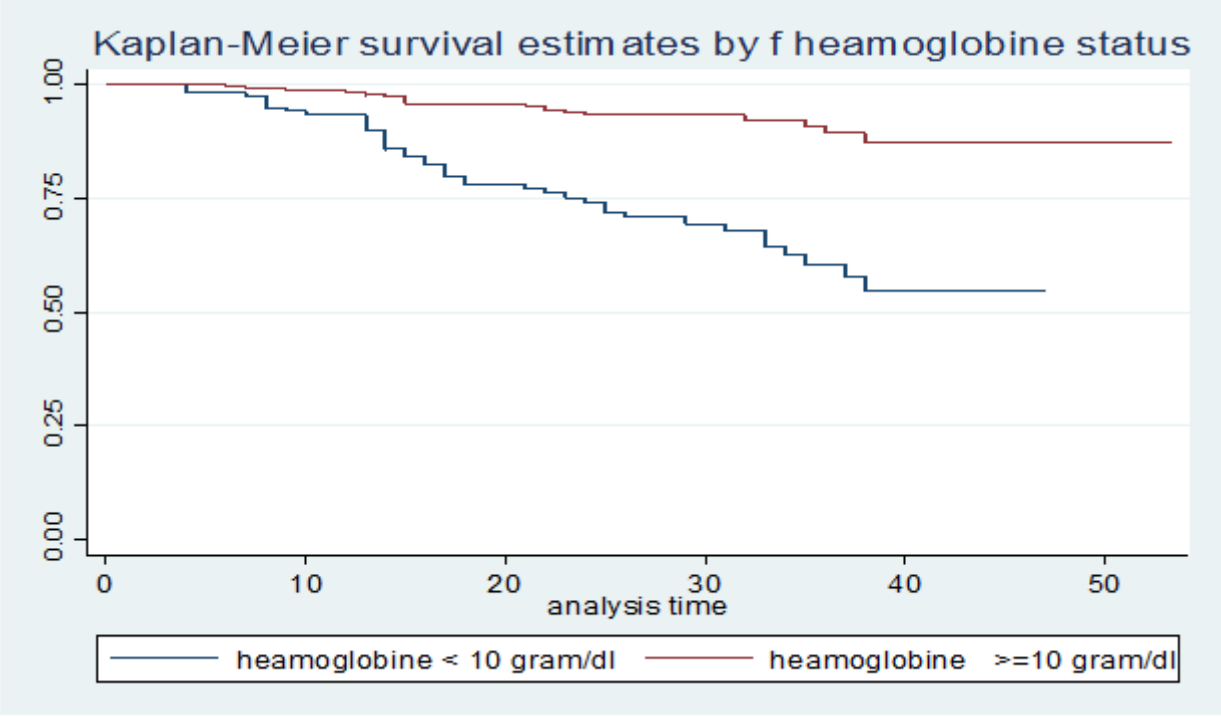

Figure 4

Kaplan Meier survival estimate on Hemoglobin in HIV infected children at Assosa and Pawe general hospitals from (1/1/2009- 30/12/2019)

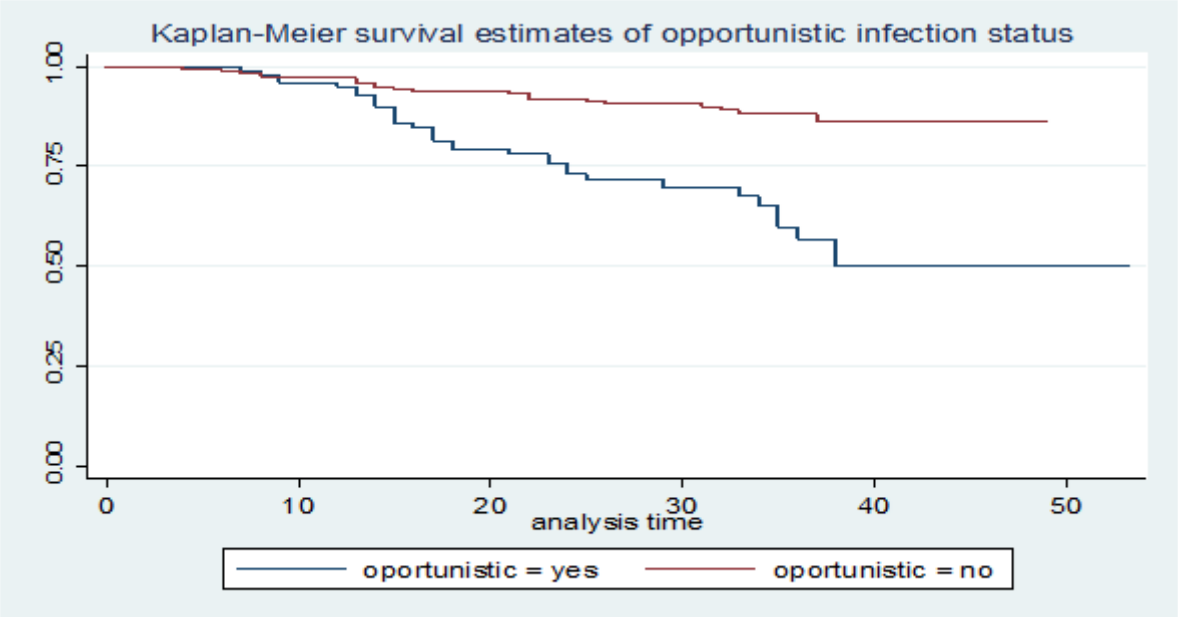

Figure 5

Kaplan Meier survival estimate on previous opportunistic infection, in HIV infected children at Assosa and Pawe general hospitals from (1/1/2009- 30/12/2019

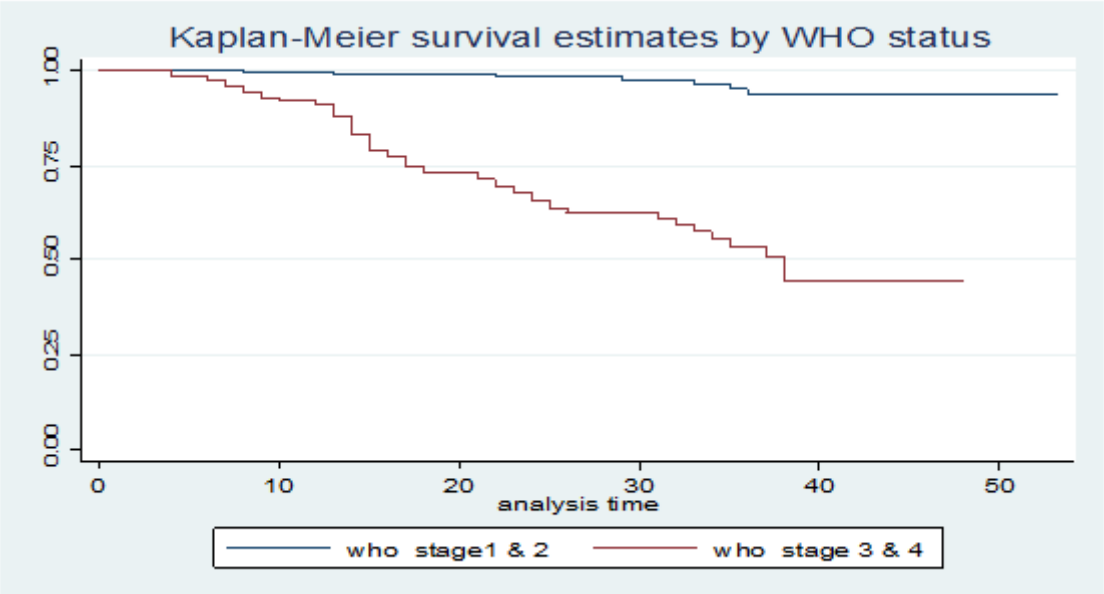

Figure 6

Kaplan Meier survival estimate based on who stage in HIV infected children at Assosa and Pawe general hospitals from (1/1/2009- 30/12/2019

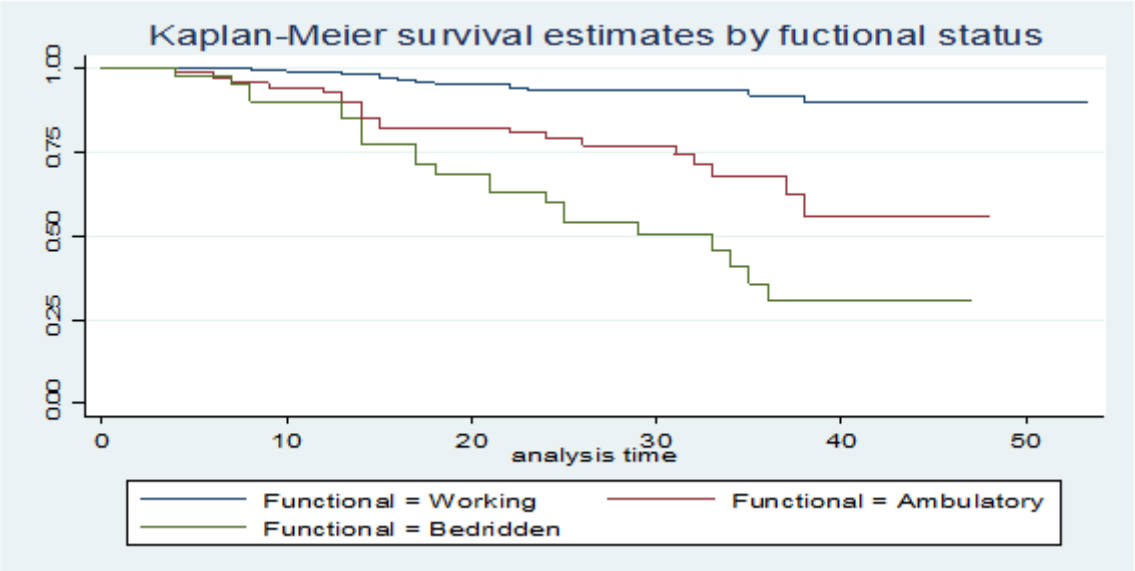

Figure 7

Kaplan Meier survival estimate based on Functional status, in HIV infected children at Assosa and Pawe general hospitals from (1/1/2009- 30/12/2019