ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF NURSING AND MIDWIFERY

DEPARTMENT OF NURSING

SURVIVAL AND PREDICTORS OF MORTALITY AMONG TB-HIV CO-INFECTED CHILDREN ATTENDING ANTI RETROVIRAL THERAPY CLINICS OF SELECTED PUBLIC HOSPITALS IN SNNPR, ETHIOPIA,2020: A RETROSPECTIVE COHORT STUDY

A THESIS TO BE SUBMITTED TO ADDISABABA UNIVERSITY, COLLEGE OF HEALTH SCIENCE, SCHOOL OF NURSING AND MIDWIFERY FOR THE PARTIAL FULFILMENT OF THE REQUIREMENTS FOR DEGREE OF MASTERS OF SCIENCE IN PEDIATRICS AND CHILD HEALTH NURSING

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APPROVAL SHEET

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I, the undersigned MSc student, declare that I have submitted my original work on a title survival and predictors of mortality among TB-HIV co-infected children attending anti-retroviral therapy clinics of selected public hospitals in SNNPR, Ethiopia 2020 for the examination.

Submitted by:

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This thesis work has been submitted for examination with my approval as an advisor.

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APPROVAL BY THE BOARD OF EXAMINATION

This thesis by Jifare Gemechu is accepted in its present form by the board of examiners as satisfying thesis requirement for the degree of masters in pediatrics and child health nursing.

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ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AAU	Addis Ababa University
ABC	Abacavir
AHR	Adjusted Hazard ratio
AOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
AZT	Zidovudine
CPT	Co-trimoxazole preventive therapy
D4T	Stavudine
EFV	Efavirenz
Hgb	Hemoglobin
HIV	Human immune virus
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution Inflammatory syndrome
MDR-TB	Multi drug resistant tuberculosis
NNRTIs	Non-nucleotide reverse transcriptase inhibitors
NRTIs	Nucleotide reverse transcriptase inhibitors
NVP	Nevirapine
OI	Opportunistic infection
SD	Standard deviation
SDG	Sustainable developmental goal
SPSS	Statistical Package for Social Sciences
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	The joint united nations program on HIV and AIDS
WAZ	Weight for age Z
WHO	World health organization

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ABSTRACT

Background: TB/HIV co-infection poses a great impact to public health. TB is the most common opportunistic infection and the most common cause of mortality in HIV infected children around the globe. But there is scarceness of studies concerning the predictors of mortality among TB-HIV co-infected children.

Objective: To assess the survival and predictors of mortality among TB-HIV co-infected children attending ART clinics of public hospitals in SNNPR, Ethiopia from 2009-2019**.**

Methods: Hospital-based retrospective cohort study was employed from January 1st, 2009 to December 31st2019 among 284 TB-HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia. Then, medical records were reviewed using a structured data extraction tool. Data were entered using Epidata 4.6 and analyzed using SPSS version 23. The Kaplan Meier survival curve along with log rank tests was used to estimate and compare survival time. Bi variable and multivariable Cox regression were conducted to identify predictors of mortality among TB/HIV co-infected children. Adjusted Hazard Ratio with its 95% confidence interval was used to estimate the strength of association and P-value ≤ 0.05 was considered as statistically significant.

Result: A total of 284 TB/HIV co-infected children were included in the study. Among these, 35 (12.3%) of them died during the study period. The overall mortality rate was 2.78 (95%CI= 1.98-3.99) per 100 child years of observation. The independent predictors of mortality were anemia (AHR=3.6; 95%CI: 1.39-9.31), fair or poor ART drug adherence (AHR=2.9; 95%CI=1.15-7.43), extra pulmonary TB **(**AHR=3.9; 95%CI: 1.34-11.45) and TB drug resistance (AHR=5.7; 95%CI: 2.07-15.96).

Conclusion: Mortality rate of TB/HIV co-infected children in selected public hospitals in SNNPR, Ethiopia was high. Moreover, anemia, drug resistant tuberculosis, extra pulmonary TB and poor adherence to ART drugs were identified as the predictors of mortality among these children.

Chapter 1 Introduction

1.1 Background

Tuberculosis (TB) is a chronic communicable bacterial infection caused mostly by *Mycobacterium tuberculosis* and rarely by *Mycobacterium Africanum*, *Mycobacterium Canetti*, or *Mycobacterium Bovis*(1).It mainly affects the lungs (pulmonary TB) but can sometimes affect other sites which is known to be extra pulmonary TB. Extra pulmonary TB includes disease of the lymph nodes, upper respiratory tract, bone, joint, heart, central nervous system, gastro intestinal, genitourinary and that distributed through blood and affect various organs like liver, spleen, skin and lung(2).

Pulmonary TB accounts for 85% of all TB cases. It can be classified as sputum smear positive or negative based on the detection of the bacteria. Positive smear cases cover 70-80% of all pulmonary TB case worldwide. TB is transmitted by inhalation of mucus droplets when infected individual releases bacteria in to the air by coughing or sneezing. Usually, the clinical manifestation in children is non-specific. But non-productive cough, fever of more than 2 weeks, weight loss, night sweat, loss of appetite, decreased activity are the common symptoms. Whereas the symptom of Extra pulmonary TB is dependent on the site affected(2).

Individuals with latent TB have five to fifteen times more risk of falling ill with TB throughout their lifetime. Persons with compromised immune systems, such as people living with human immunodeficiency (HIV), malnourished or diabetes mellitus (DM) have higher risk of developing the disease. People living with HIV have 20-37 times more probability of falling ill with active TB than those without HIV. Forty five percent of HIV negative and almost all HIV positive with TB who don’t get appropriate treatment will die(3). HIV targets the immune system and makes the defense mechanism weaker against infections. It terminates and damages the function of immune cells causing immunodeficiency. This immunodeficiency leads to increased predisposition to different infections like TB(3).

Acquired immune deficiency syndrome (AIDS) was first recognized among homosexual men in the United States (US) in 1981. The etiological agent, the human immunodeficiency virus (HIV), was known in 1983.In the mid-1980s, the virus was spread to most part of the world without being noticed(4).TB/HIV co-infection poses a challenge to human survival because of the mutual impact.HIV complicates each aspect of TB including presentation, diagnosis and treatment(5).

As the viral load rises, tuberculosis speeds up the progression of HIV infection to AIDS and consequently, leads to death. On the other hand, HIV infection reduces the CD4 count leading to depressed immunity through which it enhances the activation of latent TB and increases the relapse rate of TB. Their combination increases the burden on the health system, the development of extra pulmonary TB and negative sputum smears(1).

Treating HIV/TB co-infected patients may cause complications like drug interactions, toxicity, immune reconstitution inflammatory syndrome (IRIS), and decreased plasma drug levels leading to drug resistance during treatment regardless of adherence. TB may also be over diagnosed in HIV infected children due to many diseases that appear like TB(5).Most cases of tuberculosis in HIV infected children are seen in developing countries. The diagnosis of tuberculosis in HIV-infected children may be difficult, because the reactivity of tuberculin skin test can be absent, difficulty of culture confirmation, and the resemblance of the clinical features of TB to many other HIV-related infections. TB in HIV infected children often occurs in extra pulmonary sites. It is mostly severe and progressive. Disease recurrence is also more frequent in these children. Moreover, the mortality rate in TB/HIV co-infected children is higher especially in those with decreased CD4 count(2). Therefore, this study aimed to explore the magnitude and predictors of mortality among TB/HIV co-infected children.

1.2 Statement of the problem

Globally, an estimated 10 million people fell ill with TB in 2018 and 1.5 million died from the disease of this, 251,000 are HIV positive. Children accounted for 11% of the total mortality. The burden of disease diverges hugely among countries, from less than five to more than 500 new cases per 100,000 populations per year, with the global average of 130. Most of the TB cases in the above report occurred in WHO regions of Asia, Africa, and the western pacific accounting for 44%, 24% and 18% respectively(6). On the other hand, according to the joint United Nations program on HIV and AIDS (UNAIDS) 2018 report, an estimated 74.9 million people become infected with HIV and 32 million people have died because of AIDS related illness since the start of the epidemic. In 2018, 37.9 million people were living with HIV globally. Among these, 1.7 million were children <15 years and estimated 84,000 newly infected children were living in eastern and southern Africa(7). Particularly, the Ethiopia Population-based HIV Impact Assessment (EPHIA) reported that the prevalence of HIV among the age group 0-14 in urban Ethiopia in 2018 was 0.3%(8).

TB/HIV co-infection poses a big challenge to human survival because of the mutual impact. An estimated 8.6% of the incident TB cases in 2018 were among people living with HIV. The proportion of TB/HIV co-infection cases was highest in countries in the World Health Organization (WHO) African Region, exceeding 50% in parts of southern Africa. A total of 477,461 TB cases among HIV-positive people were reported, of which 86% were on antiretroviral therapy(6). According to WHO report, there was 17% of mortality among TB/HIV co-infected children(9).

Ethiopia is among the top 20 of the 30 high burden countries and classified as having high burden of TB, MDR/TB and TB/HIV. WHO estimated that, the prevalence of TB in Ethiopia in 2018 was 151/100,000 and the mortality rate among the HIV was 2% ranging from 1.4- 2.8 %(10). TB continued to be the major cause of morbidity and mortality among people living with HIV especially in low socioeconomic countries including Ethiopia. WHO reported that it is responsible for 1 in 3 HIV associated deaths(3). It is also the most common opportunistic infection in children living with HIV and remained among the top 10 causes of mortality in Ethiopia. In high HIV prevalent countries such as Ethiopia, HIV associated TB is increasing even in well-established TB program causing a deadly synergy(11).

Different integrated programs have been designed and implemented to prevent, diagnose and treat TB among HIV positives. However, the problem continues to be of a great concern and remains a major global and national health problem that needs extensive action to meet the goals set in SDG and Stop TB strategies(12).

The deaths of HIV/TB co-infected children have several socioeconomic impacts. Different factors contribute to mortality of TB/HIV co-infected children. Some of them are young age specially those under one year of age, being anemic, milliary pattern TB, WHO HIV stage III/IV, severe immune suppression, Co-trimoxazole preventive therapy (CPT), Isoniazid preventive therapy (IPT) and adherence to Anti retro viral drugs (ARV)(13–17) .Even though there are studies done on predictors of mortality in TB/HIV co-infected adults, there were only few previous studies done in the pediatric age group as far as the literature search showed(18–21). This study will fill the knowledge gap in the area. Furthermore, even if one study was conducted in Gondar, Ethiopia it did not include some variables that are found in other studies like TB drug resistance and previous history of TB. Therefore, this study will bridge this information gap and update the previous knowledge on the same problem.

1.3Significance of the study

The findings of this study will benefit the regional health bureau to improve and strengthen strategies related to prevention and management of TB, HIV and TB/HIV co-infection. It will also add to the existing body of knowledge which could help policy makers to implement alternative intervention strategies. Furthermore, this study will help different stakeholders of federal and regional offices to identify the predictors of mortality among TB/HIV co-infected children and modify prevention and treatment strategies accordingly. Finally, it will add reliable information for researchers who are interested in this area.

Chapter 2, Literature review

2.1 Mortality among TB/HIV co-infected children

A retrospective cohort study conducted in England and Ireland among HIV infected children identified that 9% of mortality was due to TB(22). A systematic review and meta-analysis conducted on MDR-TB/HIV co-infected children in India, in the year 2015 showed that, the mortality rate among these children was 11.5%(23). Similarly, a study in India which was conducted on MDR/TB and HIV co-infected adolescents showed mortality of 36.5% (24). Another study done in Thailand showed that the mortality of TB incident cases among children on ART was 30%(15).

A retrospective cohort study conducted among TB/HIV co-infected children in regions of Asia and Africa showed 38% of mortality. An observational study done in four countries (Burkina Faso, Cambodia, Cameron, Vietnam) indicated 19% mortality among children on ART infected with TB. Among these, 54% died during the first month of follow up(25). On the other hand, the study conducted in six countries including Botswana, Lesotho, Malawi, Tanzania, Uganda and Eswatini showed 10% death among children on ART who were infected with TB(26). Retrospective studies conducted in Nigeria showed 11.2% and 2.4% of children died due to TB/HIV co-infection while they were on treatment(27,28). Another retrospective cohort study done in Nigeria reported the death of 6.2% of children with HIV/TB co-infection , the mortality rate being 1.4 per 100 child- years of follow up(29). Additional study in Nigeria conducted among children on ART who were TB/HIV co-infected compared with those without TB showed that the mortality rate was 8 per 100 person years among TB-HIV co-infected compared to 2.3 per 100 person years among non-infected(30).

A retrospective cohort study conducted in Malawi among TB/HIV co-infected children revealed 14.4% of mortality(31). Another retrospective cohort study done in south Africa showed 11% of mortality among MDR-TB and HIV co-infected children(32). Additional study in south Africa that was conducted on children with tuberculosis displayed 14% mortality among those with HIV infection(33). Another retrospective study in South Africa which was conducted on HIV infected children who are on ART drugs revealed 8.7% of mortality. Among these, 29.7% of the children died due to TB/HIV co-infection(34). Moreover, a retrospective cohort study done in South Africa among children infected with drug resistant TB showed that 20.6% of HIV infected children died due to the co-infection(35). A retrospective cohort study from Cameroon that was

conducted on HIV positive children showed 9.9% death of which 22.72% were co-infected with TB (36). On the other hand, a retrospective cohort study in Uganda that was conducted on HIV positive children attending ART clinic who are co-infected with TB showed 10.6% of mortality (14). In addition, a cross-sectional study in Congo showed high mortality among TB/HIV co-infected children which was 47.4% compared with those without HIV infection which is 17.2% (13). Moreover, a retrospective cohort study in Ghana done among children diagnosed with TB identified 12.6% of mortality because of HIV(37). Furthermore, a retrospective cohort study in Kenya conducted on children infected with tuberculosis reported 9% of mortality among HIV positive children who were on ART and 12% of mortality among those who were not on ART(34). In Ethiopia, 14.2% mortality was showed by a retrospective cohort study which was conducted on TB/HIV co-infected children attending ART clinic of university of Gondar comprehensive specialized hospital (17).

Overall, the above studies that are done around the world showed different proportion of mortality among TB/HIV co-infected children varying from 2.4% to 47.4%. This figure shows a huge difference between different setups. Furthermore, studies with high prevalence rates are classified under high burden countries according to WHO clinical stage.

2.2 Predictors of mortality in TB/HIV co-infected children

2.2.1 Socio demographic predictors

Several studies showed that socio demographic factors have association with the mortality of children with TB/HIV co-infection (26,29,31). According to many studies, children who are younger than one year of age have taken the highest proportion of death than older children. An observational study done in four countries (Burkina Faso, Cambodia, Cameron, Vietnam) indicated that those children younger than 2 years have strong association with mortality(26). However, a cross-sectional study done in Congo included under five children as having greater risk of mortality as compared to older children(13). Overall, the lower the age of a child with TB-HIV co-infection, the higher the mortality would be.

A retrospective cohort study conducted in Malawi identified male sex as a predictor of mortality among TB/HIV co-infected children(31). In addition, prospective cohort study done among TB/HIV co-infected children in Tanzania indicated that children living in low socio demographic area have association with mortality(16).

2.2.2 Child clinical characteristics

Child Clinical characteristics including WHO stage, CD4 level, Hemoglobin level, Site of TB and Presence of opportunistic infection are predictors of mortality among TB/HIV co-infected children(16,17,26,38). A retrospective cohort study conducted in Malawi and a prospective cohort study done among TB/HIV co-infected children in Tanzania showed that children with advanced WHO clinical stages that is stage III and IV are highly at risk of mortality(16,31). On the other hand, severe immune suppression predicts the death of these children. The study from four African countries identified high mortality in children with CD4 levels less than 10%(26). Moreover, the retrospective study in Malawi identified six times more risk of mortality of severely immune suppressed children than those with no immune suppression(31).

Hemoglobin level is another predictor of mortality in TB/HIV co-infected children. A prospective cohort study done in Tanzania and retrospective cohort study in Gondar conducted on TB/HIV co-infected children stated that children with severe anemia or those with low hemoglobin level (≤8 g/dl) are more likely to die than those with normal hemoglobin levels(16,17).

Miliary disease is one form of extra pulmonary TB. It is disseminated form of tuberculosis that is caused when the bacteria are spread to two or more organs through the blood leading to severe form of the disease(2). An observational study done in four countries (Burkina Faso, Cambodia, Cameron, Vietnam) showed that, miliary radiographic pattern predicts the mortality of co-infected children(26). On the other hand, retrospective observational cohort studies done in Nigeria, south Africa and Gondar specialized comprehensive hospital identified extra pulmonary TB as one of the predictors(17,25,32). The study in Nigeria also stated that miliary TB takes the highest risk among the extra pulmonary forms(32).

Severe immune suppression in children living with HIV gives chance for opportunistic infections to take place. Recurrent bacterial infections are common in these children which further deteriorates their immunity(2). Therefore, having opportunistic infection leads to mortality of TB/HIV co-infected children(16,17).

2.2.3 Follow up characteristics

A package of care is delivered for people living with HIV. This package of care includes, screening and diagnosis of opportunistic infections, providing prophylactic and preventive

treatments like co-trimoxazole and isoniazid preventive therapies, ART initiation and adherence support(39).

Studies ruled out that, children with TB/HIV co-infection who started ART two months after TB diagnosis are prone to mortality(30,31). Furthermore, those children who are previously infected with tuberculosis have higher chance of dying than those with new infection(40). In addition, the study done in Ethiopia indicated that not taking co-trimoxazole and isoniazid preventive therapy during the follow up times will expose the child for early death(17).

In summary, the mortality of TB/HIV co-infected children is attributed to different factors. According to the above studies, socio demographic factors like young age and sex can predict it. In addition, clinical characteristics including advanced WHO clinical stages, severe immune suppression, anemia, and extra-pulmonary tuberculosis mainly disseminated TB and the presence of additional opportunistic infections are predictors of mortality. At last, follow up characteristics like history of previous TB, not taking IPT and CPT are factors associated with mortality.

Conceptual Frame Work

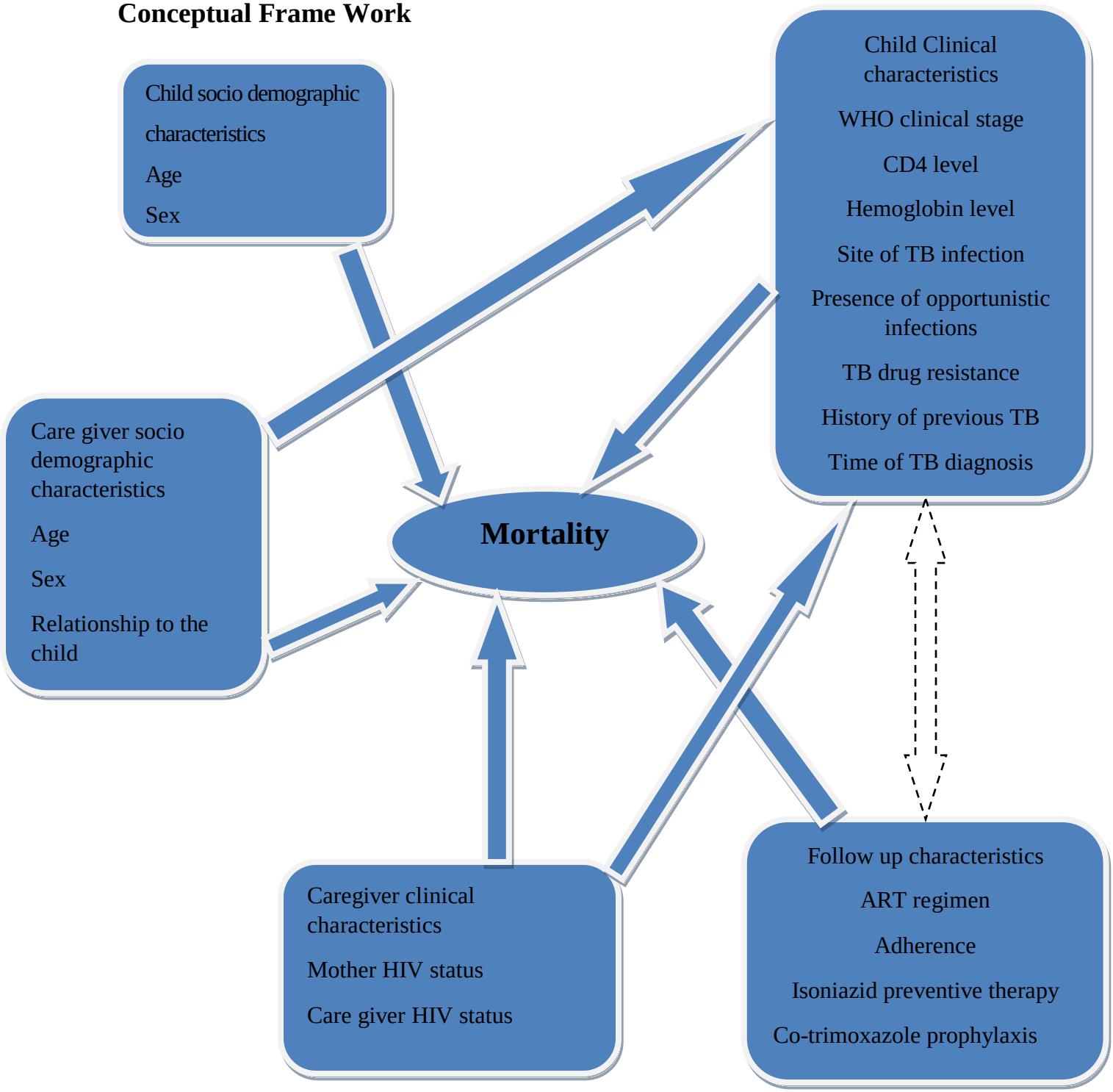

Figure 1 Conceptual frame work showing Predictors of mortality in TB/HIV co-infected children (developed from literatures)(16,17,29)

Chapter 3: Objectives

General Objective:

- To assess survival and predictors of mortality among TB-HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia from January 1st2009- December 31st2019

Specific Objectives:

- To estimate incidence of death among TB/HIV co-infected children attending ART clinic
- To estimate time to death of TB/HIV co-infected children attending ART clinic
- To identify predictors of mortality among TB/HIV co-infected children attending ART clinic

Chapter 4: Method and Materials

4.1 Study Area and Period

The data was extracted from February to May, 2020 in ART clinics of selected public hospitals in Sothern Nation's nationalities and peoples region (SNNPR), Ethiopia. SNNPR is one of the administrative regions in Ethiopia. It is the third largest region in area out of nine administrative regions in Ethiopia. It is also the most diverse region in the country in terms of culture, language and ethnicity. It is sub divided in to 14 zones, one city administration and four special woredas. Hawassa is its administrative town of the region located 273 km from Addis Ababa the capital city of Ethiopia. According to the 2007 census, the region had an estimated population of 18.9 million. There are four referral hospitals and forty general hospitals in the region.

From these, six hospitals, three referral (Hawasa university referral hospital, Wolaita Sodo University teaching referral hospital and Nigist Eleni Mohammad memorial referral hospital) and three general hospitals (Yirgalem, Arba Minch and Jinka) were included in the study.

4.2 Study Design

A hospital-based retrospective cohort study design was employed in ART clinics of selected public hospitals in SNNPR, Ethiopia

4.3 Population

4.3.1 Source Population

The source population was all TB/HIV co-infected children under 15 years age ever enrolled in pediatrics ART clinics of selected public hospitals in SNNPR.

4.3.2. Study Populations

All selected TB/HIV co-infected children under the age of 15 who were and registered on HIV care from January 1st, 2009 to December 31st2019.

4.3.3 Inclusion criteria

All charts of children with TB/HIV co-infection who were less than 15 years of age and enrolled to ART clinics of selected public hospitals in SNNPR were included.

4.3.4 Exclusion Criteria

Charts of Study participants with incomplete information of important study variables like WHO clinical stage, hemoglobin level, CD4 level, drug resistance status

4.4. Sample size determination and sampling procedures

4.4.1 Sample size determination

Since the number of TB/HIV co-infected children was small all charts of the children which fulfilled the inclusion criteria were included in the study. A total of 325 charts of TB/HIV co-infected children were identified from ART register books of the selected hospitals but only 284 charts were finally included the study.

4.4.2 Sampling Procedure

The study was conducted at selected public hospitals in SNNPR. Purposive sampling was used to select the hospitals with high patient volume. Then, medical record numbers of children who are TB/HIV co-infected and on ART from January 1st, 2009 to December 31, 2019 were identified. The ART log book was used to look for those with history of tuberculosis. Then, since the number of the co-infected children in the selected hospitals was manageable, all of the children's charts which fulfilled the inclusion criteria were included in the study. From 325 identified charts, 284 charts were finally selected. The rest of the charts were excluded due to incompleteness.

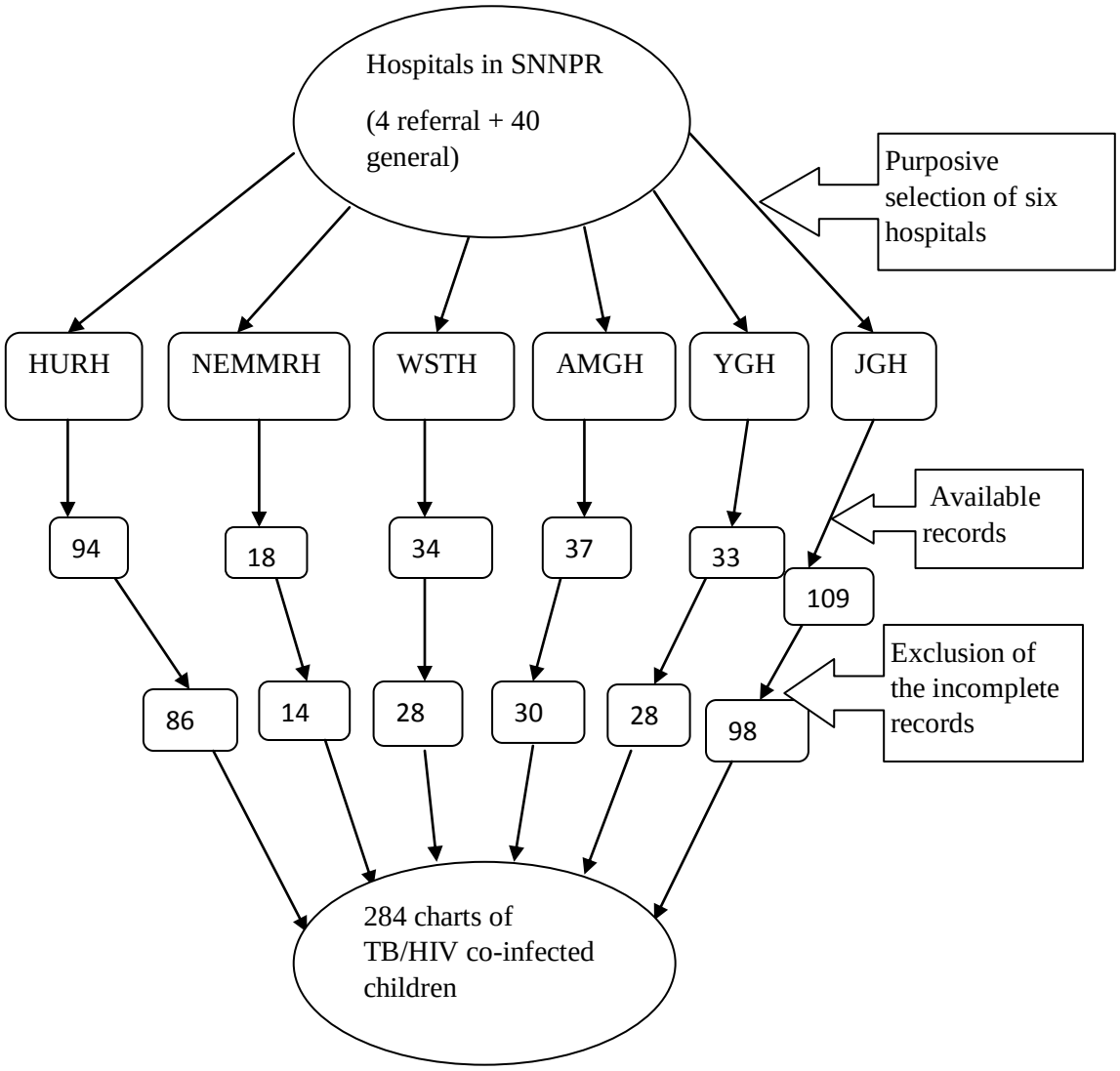

Figure 2 Schematic presentation of sampling procedure

4.5 Study Variables

4.5.1 Dependent variable

Time to death of TB/HIV co-infected children

4.5.2 Independent Variables

Socio demographic characteristics of the child – Age, sex

Clinical characteristics- CD4 cell count, hemoglobin level, WHO stage, opportunistic infections, site of TB, time of TB diagnosis, TB drug resistance, previous history of TB

Follow up characteristics- ART regimen, Adherence, co-trimoxazole prophylaxis, Isoniazid preventive therapy,

4.6 Standard and operational definitions

Event- death of a child

ART adherence- classified as Good, Fair and Poor according to calculated percentage of ART drug taken from the total monthly dosage

Good: Miss≤3 doses per month

Fair: Miss 4-8 doses

Poor: Miss> 9 doses

Loss to Follow Up- When the child misses appointment for more than three months

Transferred Out- when a child is transferred to other health facility

Treatment Failure- classified by clinical criteria, immunologic criteria and virologic criteria

Clinical Treatment Failure is the detection of new or recurrent WHO clinical stage of III or IV

Immunologic Treatment Failure is a drop in CD4 level, after the initial immune recovery next to ART initiation to values at or below the age-related CD4 threshold for treatment initiation OR 30% drop of CD4% or value from highest levels after therapy.

Virologic Failure– persistent viral load exceeding 5000 copies/ml in a child who is fully adhered to treatment and who was on ART for at least 24 weeks.

Time to death- the time between the diagnosis of TB/HIV co-infection and occurrence of the event (death) during the follow up period

Censored- If the child is loss to follow up or transferred out before developing the event or if the child is alive at the end of the study period

Drug resistant TB; classified in to Multi drug resistant (MDR) and Extensive drug resistant (XDR)

MDR – resistance to isoniazid and rifampicin

XDR- resistance to at least four core anti TB drugs involving isoniazid, rifampicin, any of the fluroquinolons like moxifloxacin orlevofloxacin and to at least one of the second line drugs which are amicacin, capreomaycin or kanamycin

Baseline Information; an initial measurement of values at first contact

Immune suppression-Based on WHO classification

Table 1 Immune suppression-Based on WHO classification

HIV-associated immunodeficiency	**Age-related CD4+ values**			
	<11 months (%CD4+)	**12–35 months (%CD4+)**	**36–59 months (%CD4+)**	**>5 years (absolute number per mm3 or %CD4+)**
None or not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350−499
Advanced	25–29	20–24	15−19	200−349
Severe	<25	<20	<15	<200 or <15%

4.7 Data Collection Procedure

4.7.1 Data Collection Tool and Procedure

A data extraction tool was developed from the national ART entry and follow up form that is currently used by the ART clinics of the study area. It comprises socio demographic characteristics, clinical characteristics, TB related and ART follow up. The data was collected by six BSc and five diploma nurses working in the ART clinic of respective hospitals. They used the data collection tool to extract the information from children's charts. Charts were collected by using the children's registration number which was found in the data base computer system. In addition, data clerks helped in identifying the charts.

4.7.2 Data quality control

The data extraction tool was carefully adapted from the national follow-up care forms and some articles. It was pre tested to check the consistency**.** Training was given for data collectors regarding the objectives and variables of the study and how to extract data by using the tool for one day. Completeness of each collected data was audited at the end of each day by the principal investigator and supervisor in order to correct it until the end of collection process. Moreover, a periodic supervision took place.

4.8 Data Processing and Analysis

Before data entry, all questionnaires were checked for completeness. Cleaned and coded data was entered into Epi Data version 4.6 and analysis of the data was conducted by using the statistical package for social sciences (SPSS) version 23. Cox proportional hazard model assumption was checked using Schoenfeld, residual test. Patients' cohort characteristics for continuous data were described in terms of central tendency (mean or median) and dispersion (standard deviation or inter quartile range). Frequency distribution was used for categorical data. The Kaplan Meier survival curve was used to estimate and compare survival time and log rank tests was used to compare survival curves. Bi variate Cox- regression model was fitted for each explanatory variable and the variables with significance level of $p \leq 0.25$ were included in the multivariable Cox model to identify independent predictors of mortality among TB/HIV co-infected children. Adjusted Hazard Ratio with its 95% confidence interval was used to estimate the strength and direction of association and p value ≤ 0.05 was considered as statistically significant.

4.9 Ethical Considerations

Ethical clearance was sought and obtained from Institutional Review board of Addis Ababa University, College of Health sciences, School of Nursing and Midwifery. Permission to conduct the study was obtained from Zonal and District Health offices. A formal letter was submitted to the respective hospitals. Since the study was done through reviewing of medical records, the individual patients may not be harmed as long as the confidentiality is kept. Confidentiality was kept by coding all the collected data. Moreover, the charts were locked in a separate room before it was entered in to the computer. After entering the data, the computer was locked by password. Names and unique ART numbers were not included in data collection format and the data was not disclosed to any person other than principal investigator. All information collected from patients' cards was kept strictly confidential and names of patients on ART were not included in the checklist.

4.10 Dissemination Plan

The result of the study will be presented and submitted to Addis Ababa University, College of health science, School of Nursing and Midwifery. The findings will be distributed to Health departments of the respective town and other organizations working on related area. The finding of the study will be presented in national and international scientific conferences. Attempt will be made to publish the finding in scientific and peer reviewed journal.

5. Results

5.1 Socio demographic characteristics

A total of 325 charts of children on ART and had a history of tuberculosis were reviewed. However, 41 charts were excluded from analysis due to incomplete data. Therefore, 284 charts of children with TB/HIV co-infection were included in the analysis. Among these, almost half (48.2%) were male. Around half of the children (47.9%) were with the age group of 6-10 years. The mean (SD) age of the study participants was 7.1(3.7) years. Almost two-third (74.6%) of the children's care givers were HIV positive. In addition, 46.8% of the child's care givers were with the age group of 25-34 years.

Table 2 Socio-demographic characteristics of TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia, from January 2009 to December 2019

CHARACTERISTICS		Total n (%)	Censored n (%)	Death n (%)
Age	<1	18(6.3)	17(94.4)	1(5.6)
	1-5	78(27.5)	68(87.2)	10(12.8)
	6-10	136(47.9)	116(85.3)	20(14.7)
	11-15	52(18.3)	48(92.3)	4(7.7)
Sex	Male	137(48.2)	121(87.1)	16(11.7)
	Female	147(51.8)	128(88.3)	19(12.9)
Age of care giver	15-24	40(14.1)	36(90)	4(10)
	25-34	133(46.8)	114(85.7)	19(14.3)
	35-44	82(28.9)	74(90.2)	8(9.8)
	>44	29(10.2)	25(86.2)	4(13.8)
Child lives with	Parents	239(84.2)	210(97.9)	29(12.1)
	Guardian	17(6)	16(94.1)	1(5.9)
	Orphan	9(3.2)	6(66.7)	3(33.3)
	Others	19(6.7)	17(89.5)	2(10.5)
Child care giver	Mother	186(65.5)	162(87.1)	24(12.9)
	Father	35(12.3)	30(85.7)	5(14.3)

	Step parent	11(3.9)	10(90.9)	1(9.1)
	Sibling	17(6)	17(100)	0(0)
	Grand **parents**	22(7.7)	19(86.3)	3(13.6)
	Others	13(4.5)	11(84.6)	2(15.3)
Mother HIV status	Positive	223(77.8)	191(85.7)	32(14.3)
	Negative	3(1.1)	3(100)	0(0)
	Unknown	58(20.4)	55(94.8)	3(5.2)
Care giver HIV status	Positive	212(74.6)	183(86.3)	29(13.7)
	Negative	28(9.9)	27(96.4)	1(3.6)
	Unknown	44(15.5)	39(88.6)	5(11.4)

5.2 Child clinical characteristics

From the total participants, majority of them (91.9%) had opportunistic infection at baseline. Out of this, pulmonary TB contributes the highest which was, 63% followed by pneumonia (17.3%) and diarrhea (9.9%). 224 (78.9%) children were classified under WHO stage 3 & 4 at baseline. Moreover, 16.4% and 23.4% of the children had advanced and severe immune suppression respectively. Almost half (41.2%) of the children were eligible for HAART by WHO stage criteria. Around (14.1%) of the children had treatment failure. But only 24 of them were on second line ART drug. Regarding prophylaxis use, majority (91.5%) of them had taken co-trimoxazole preventive therapy and 64.1% of the study participants had taken Isoniazid preventive therapy.

Table 3 Clinical characteristics of TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia, from January 2009 to December 2019

Variable	Category	**Total** **n (%)**	**Censored** **n (%)**	**Dead** **n (%)**
Baseline WHO stage	I & II	60(21.1)	56(93.3)	4(6.7)
	III & IV	224(78.9)	193(86.2)	31(13.8)
ART eligibility criteria	CD4+ cells	12(4.2)	12(100)	0(0)
	WHO stage	117(41.2)	109(93.2)	8(6.8)
	Both	78(27.5)	62(79.5)	16(20.5)
	Test and treat	74(26.05)	64(86.4)	10(13.5)
	Not recorded	3(1.05)	2(66.6)	1(33.3)
Baseline Opportunistic infection	Yes	261(91.9)	229(87.7)	32(12.3)
	No	23(8.1)	20(87)	3(13)
Initial regimen	D4T based	147(51.8)	129(87.8)	18(12.2)
	AZT based	104(36.6)	90(86.5)	14(13.5)
	TDF based	16(5.6)	15(93.8)	1(6.2)
	ABC based & 1j	17(6)	15(88.2)	2(11.8)
Initial regimen change	Yes	135(47.5)	121(89.6)	14(10.4)
	No	149(52.5)	128(85.9)	21(14.1)
Reason for regimen change	Side effect	33(11.6)	29(87.9)	4(12.1)
	Treatment failure	24(8.5)	20(83.3)	4(16.7)
	TB	30(10.6)	27(90)	3(10)
	Stock out	35(12.3)	32(91.4)	3(8.6)
Treatment failure	Yes	40(14.1)	37(92.5)	3(7.5)
	No	244(85.9)	212(86.9)	32(13.5)
Baseline HIV related immune suppression	Mild/non significant	172(60.6)	164(95.3)	8(4.7)

	Advanced	46(16.2)	40(87)	6(13)
	Severe	66(23.2)	45(68.2)	21(31.8)
INH	Yes	182(64.1)	163(89.6)	19(10.4)
	No	102(35.9)	86(84.3)	16(15.7)
CPT	Yes	260(91.5)	227(87.3)	33(12.3)
	No	24(8.5)	22(91.7)	2(8.3)
Baseline hemoglobin	≤10	104(36.6)	89(76.7)	27(23.3)
	>10	180(63.4)	160(95.2)	8(4.8)
Adherence	Good	266(93.7)	238(89.5)	28(10.5)
	Fair/poor	18(6.4)	11(61.1)	7(38.9)
Site of TB	Pulmonary	218(76.8)	232(90.3)	25(9.7)
	Extra pulmonary	66(23.2)	17(63)	10(33)
Time of TB diagnosis	Pre ART	171(60.3)	153(89.5)	18(10.5)
	ART	113(39.8)	96(85)	17(15)
Previous history of TB	Yes	42(14.8)	29(69)	13(31)
	No	242(85.2)	220(90.9)	22(9.1)
TB drug resistance	No	264(93)	237(89.8)	27(10.2)
	MDR	20(7)	12(60)	8(40)

5.3 Mortality rate

284 children with TB/HIV co-infection and on ART follow up were followed for different period of time with total of 1257.17 child-years of observation. They were followed for a minimum of one month to a maximum of 10 years. The median follow-up time was 4.5 years. A total of 35(12.3%) deaths were observed through the follow up time making the overall mortality rate to be 2.78 per 100-person year of follow up (95%CI= 1.98-3.99) for the study cohort. From those who died, 16(45.78%) of them were male, 60% of them were WHO stage 4, 65.7% of them had CD4 level less than two hundred. The cumulative probability of survival at the end of six-month, one year, five year and ten year was 94.1%, 90.9%, 88% and 76.1% respectively.

5.4 Predictors of mortality

The equality of survival for different categories of explanatory variables was tested by Log rank (Mantel-Cox) test. Hemoglobin level, ART drug adherence, type of TB and TB drug resistance were significantly associated with time to death. The mean survival time of the whole follow-up was 8.8 (95%CI; 8.4-9.15) years.

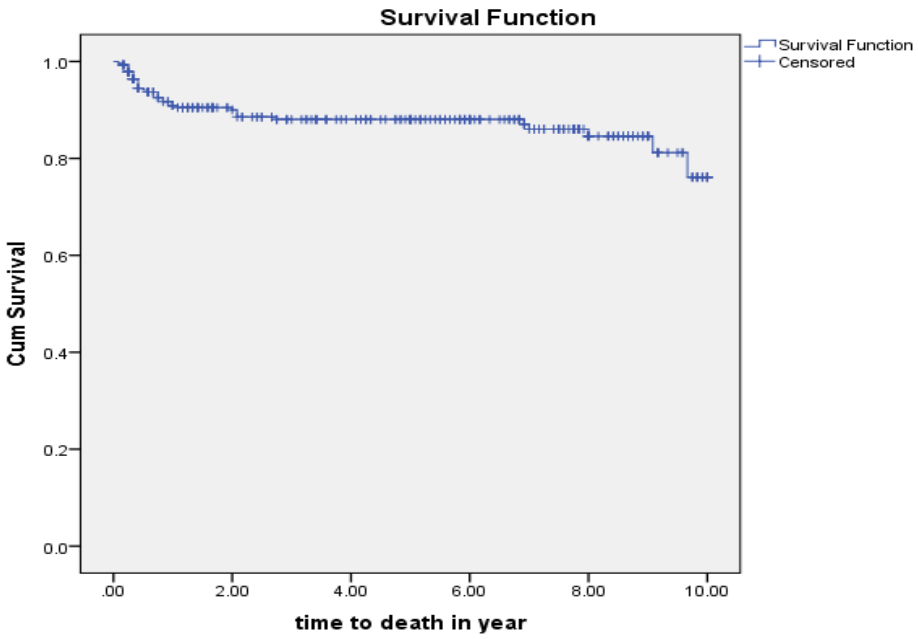

Figure 3 Kaplan-Meier curve of survival proportion for TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia, from January 2009 to December 2019

Table 4 Mean survival time and log-rank (Mantel-Cox) test survivor functions among TB/HIV co-infected children attending ART clinics of selected hospitals in SNNPR, Ethiopia from January 2009 to December 2019

Variable	Category	Mean	Log rank X^2	P- value
Time of TB occurrence	Pre- ART	9.05(8.6-9.4)	3.65	0.056
	ART	8.12(7.38-8.87)		
WHO stage at TB diagnosis	III	9.24(8.85-9.62)	11.45	0.001
	IV	7.88(7.07-8.68)		
Hemoglobin level	≤10	7.73(6.98-8.48)		
	>10	9.51(9.18-9.84)	21.05	0.001
Site of TB	Pulmonary	9.02(8.66-9.39)	17.59	0.001
	Extra pulmonary	6.45(4.72-8.18)		
TB drug resistance	No	8.98(8.62-9.34)	20.28	0.001
	MDR	5.55(3.56-7.55)		
ART drug adherence	Good	8.95(8.58-9.31)	12.71	0.001
	Fair/poor	6.28(4.19-8.36)		
Previous history of TB	Yes	6.72(5.43-8.01)		
	No	9.11(8.76-9.46)	18.84	0.001
ART treatment failure	Yes	9.22(8.37-10.06)		
	No	8.66(8.23-9.09)	1.07	0.191
Baseline PTB	Yes	8.99(8.56-9.41)		
	No	7.51(6.85-8.16)	2.84	0.092
Baseline EPTB	Yes	6.87(5.13-8.62)		
	No	8.84(8.46-9.22)	2.61	0.106
Baseline oral thrush	Yes	6.77(4.59-8.95)		
	No	8.82(8.44-9.1)	2.34	0.126
Baseline esophageal thrush	Yes	5.2(2.41-7.99)		
	No	8.81(8.43-9.19)	3.06	0.08

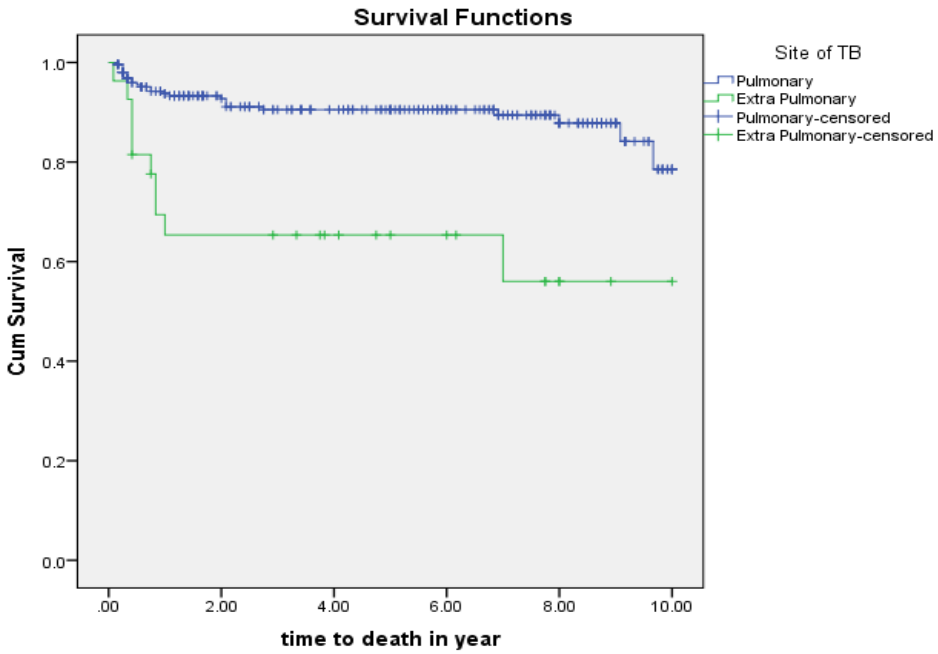

Figure 4 The Kaplan- Meier estimates of survival function by site of TB infection of TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia from January 2009 to December 2019

The mean survival time for those with extra pulmonary tuberculosis was 6.5(95%CI: 4.7-8.2) years whereas it was 9(95%CI: 8.7-9.4) years for those with pulmonary tuberculosis with significance level of p=0.0001.

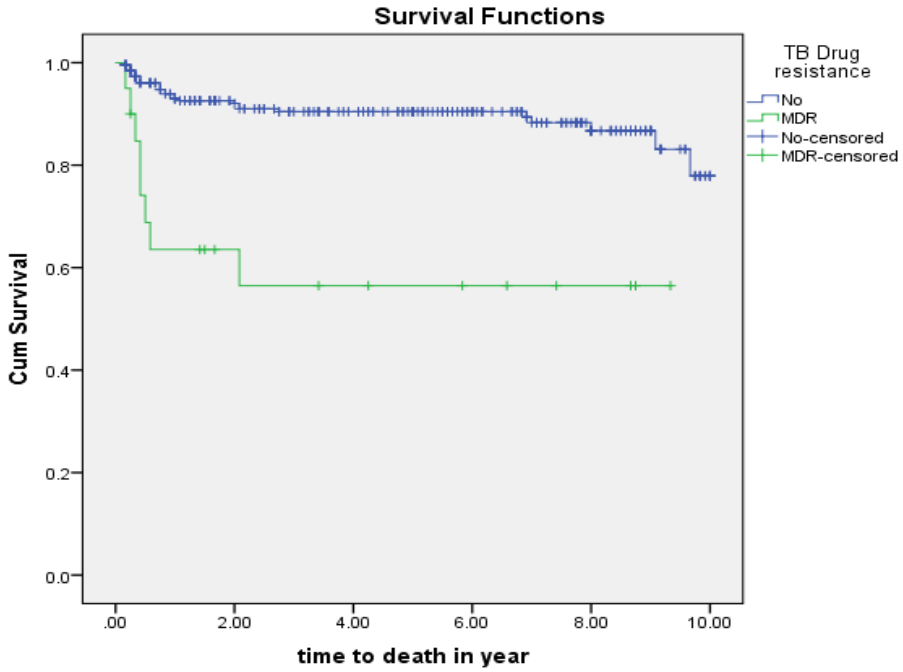

Figure 5 The Kaplan- Meier estimates of survival function by TB drug resistance status of TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia from January 2009 to December 2019

The mean survival time of those with multi drug resistant tuberculosis and HIV co-infected is lower 5.5 (95%CI: 3.5-7.5) years when compared with those with no drug resistances 8.9(95%CI: 8.6-9.3) years (p=0.001).

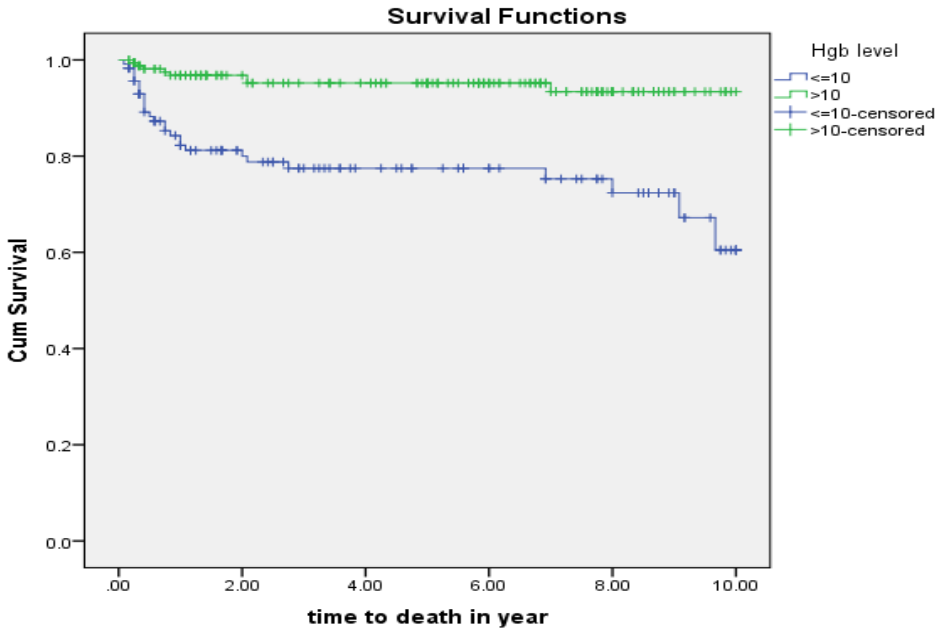

Figure 6 Kaplan –Meier survival curve of hemoglobin level of TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia from January 2009 to December 2019

The mean survival time for children with hemoglobin level≤10 g/dl was 7.73(95%CI: 6.98-8.48) years where as for those who had hemoglobin level above 10 g/dl was 9.51(95%CI: 9.18-9.84) years (p value=0.001).

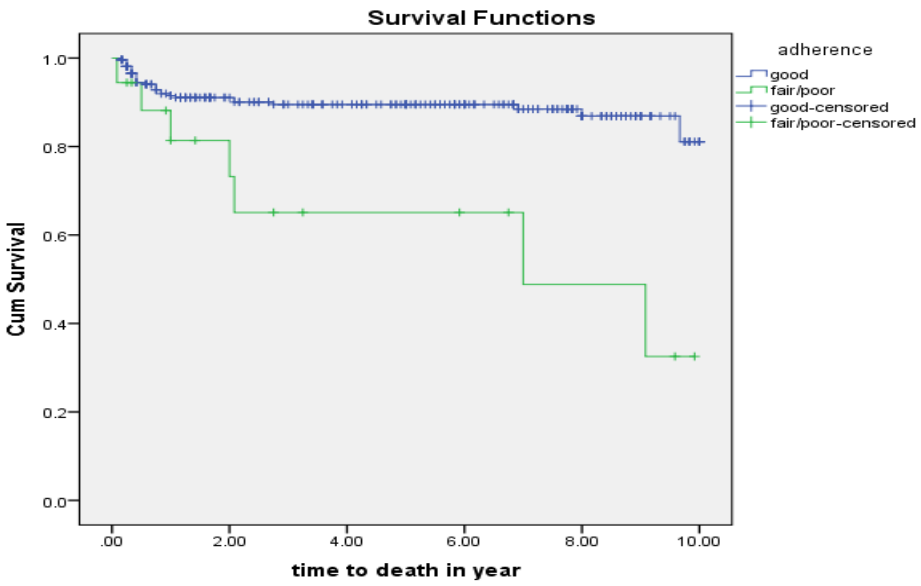

Figure 7 The Kaplan- Meier estimates of survival function by ART drug adherence of TB/HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia from January 2009 to December 2019.

Individuals who have good ART drug adherence have greater mean survival time than who had fair or poor adherence which was 8.95 (95%CI: 8.52-9.31) years compared to 6.28 (95%CI: 4.17-8.36) years (p value=0.001)

Predictors of mortality among TB/HIV co-infected children

The bi-variable Cox regression analysis showed that ART drug adherence, type of TB, previous history of TB, time of TB diagnosis, WHO stage at TB, drug resistant TB, Hemoglobin level at baseline, Isoniazid prophylaxis (IPT), presence of Pulmonary TB, extra pulmonary TB, oral and esophageal thrush at baseline, and adherence to ARV drugs were associated with mortality of TB/HIV co-infected children. But type of TB, drug resistant TB, anemia and ART drug adherence showed statistically significance and declared to be independent predictors of mortality among TB/HIV co-infected children in multivariable Cox-regression analysis.

According to this study, the risk of death for TB/HIV co-infected children with hemoglobin level of ≤10 gm/dl were almost four times higher than those with hemoglobin level of > 10 gm/dl (AHR=3.6; 95%CI: 1.39-9.31). Individuals who had drug resistant TB have almost six times at higher risk of dying than those who had no drug resistant TB (AHR=5.7;95%CI: 2.07-15.96). Children who had poor/fair adherence had three times higher risk of dying than those with good adherence (AHR=2.9; 95%CI=1.15-7.43). Moreover, those children with extra pulmonary TB

have four times higher at higher risk of dying than those with pulmonary TB **(**AHR=3.9; 95%CI: 1.34-11.45).

Table 5 Cox-regression analysis of predictors of mortality of TB/HIV co-infected children attending ART clinics of public hospitals in SNNPR, Ethiopia

Variables	Categories	Death	Censored	CHR	AHR
Time of TB diagnosis	Pre ART	18	153	0.52(0.26-1.03)	0.5(0.18-1.36)
	ART	17	96	1.00	1.00
WHO stage at TB diagnosis	III	14	169	1.00	1.00
	IV	21	80	3.0(1.53-5.95)	1.61(0.71-3.67)
Hemoglobin level	≤10mg/dl	27	89	5.23(2.37-11.54)	**3.6(1.39-9.31)***
	>10mg/dl	8	160	1.00	1.00
Site of TB	Pulmonary	25	232	1.00	1.00
	Extra pulmonary	10	17	4.2(2.02-8.81)	**3.9(1.34-11.45)***
TB drug resistance	No	27	237	1.00	1.00
	MDR	8	12	5.1(2.31-11.31)	**5.7(2.07-15.96)****
ART drug adherence	Good	28	238	1.00	1.00
	Fair/Poor	7	11	4.02(1.75-9.22)	**2.9(1.15-7.43)***
Previous history of TB	Yes	14	53	4.1(2-8.33)	2.63(0.17-6.44)
	No	21	196	1.00	1.00
ART treatment failure	Yes	3	37	0.46(0.14-1.5)	0.56(0.16-1.93)
	No	212	32	1.00	1.00
IPT	Yes	19	163	1.00	1.00
	No	16	86	1.65(0.85-3.22)	0.55(0.26-1.15)
Baseline PTB	Yes	20	159	0.55(0.27-1.14)	2.3(0.66-8.17)
	No	15	90	1.00	1.00
Baseline EPTB	Yes	4	13	2.3(0.8-6.5)	0.97(0.24-3.9)
	No	31	236	1.00	1.00
Baseline oral thrush	Yes	3	11	2.44(0.74-8.01)	3.7(0.12-13.39)
	No	32	238	1.00	1.0
Baseline esophageal thrush	Yes	2	6	3.3(0.79-13.93)	4.4(0.77-25.02)
	No	33	243	1.00	1.0

Key; CHR=crude hazard ratio AHR= adjusted hazard ratio *

6. Discussion

This hospital-based retrospective cohort study was conducted to determine magnitude of mortality and its predictors among children with TB/HIV co-infection. As a result, the mortality rate of children with TB/HIV co-infection was 2.78 per 100 child years of follow up and the proportion of mortality was 12.3% within the study population. Type of TB, drug resistant TB, hemoglobin level and ART drug adherence were the identified predictors of mortality among TB/HIV co-infected children.

Mortality rate as a result of TB/HIV co-infection in this study was high. The finding of this study is comparable a cohort study conducted in Gondar comprehensive specialized hospital which was 3.27 per 100 child years of observation (17). The reason for this might be the similarities in study participants age and national protocol in the delivery of ART care. Furthermore, the protocol for diagnosis and management of tuberculosis is also similar. On the other hand, our finding is lower than cohort study conducted in South Africa where mortality rate was 5.96 person years of follow up (38). This may be explained by the fact that the South African study was conducted only on children younger than two years of age. The higher risk of death in under two children is high because of immature immune system leading to severe disease and death.

On the other hand, our finding is a little higher than a study conducted in Nigeria which was 1.4 per 100 child years of observation (29). This may be explained by the fact that the previous study did not include children who were co-infected with extra pulmonary tuberculosis. Children with EPTB are at a greater risk of mortality due to the severity of the disease. Most of the children in this study who were co-infected with extra pulmonary TB and HIV were diagnosed with disseminated form of extra pulmonary TB which is the most severe form. In addition, the previous study was conducted over eight years which is shorter than the period by which this study conducted.

The proportion of mortality in this study which is 12.3% is comparable to the study conducted in Tanzania which was 12.4%(16). And it is in line with the studies done in Nigeria which was 13%(27), Malawi 14.4%(31), South Africa 11%(32), meta-analysis in South Africa 11.5%(23) and Uganda 10.6%(14). Furthermore, only slight difference from an observational cohort study conducted in four countries (Burkina Faso, Cameroon, Cambodia and Vietnam) 19% (25) and a study conducted in South Africa 20.6% (41). This may be due to the similarities in the burden of

HIV, TB and HIV/TB co-infection as all study areas are classified under high burden countries and the similarities in the age group of study participants may be another reason. There are also findings of studies with higher results than this study including, a system review and meta-analysis in south Africa 29.4%(23), retrospective cohort study from Thailand (30%)(42) , cohort study conducted in India (36%)(43) and cross sectional study conducted in Congo (47.7%) (13). This difference may be due to the difference in number of study participants from the study in Thailand. Furthermore, the studies from India and South Africa were conducted only on MDR TB/HIV co-infected children who are at high risk of mortality.

According to this study, the overall cumulative survival time of the study period was 76.1% which is comparable with retrospective cohort study conducted in Gondar comprehensive specialized hospital which was 79.4%(17). This may be because of the similarities in study participant's age, socio demographic characteristics and management protocols of TB, HIV and TB/HIV co-infection. The pick mortality rate in this study, which is 12.1 per 100 child-years, was observed in the first six months of follow up. The possible reason for this may be the immune reconstitution inflammatory syndrome (IRIS) which is in general abnormal immune response to antigens after the initiation of ART drugs mostly in the first six months of initiation. Moreover, in the case of TB/HIV co-infection, there may be exacerbation of signs and symptoms of tuberculosis.

The result of the multi variable analysis of this study indicates that, children who had anemia were almost four at times higher risk of mortality than those who had no anemia. This result is in line with studies conducted in Gondar, Tanzania and Thailand (15–17). The possible justification could be, low hemoglobin level in anemic children leads to decreased oxygen delivery to cells which hinders the cells ability to maintain and repair its self. This condition will add burden on the TB/HIV co-infected child leading to mortality.

Another predictor of mortality among TB/HIV co-infected children was extra pulmonary tuberculosis. Similar finding was reported by the study from Gondar comprehensive specialized hospital(17). This may be due to the extra pulmonary forms of TB are mostly more severe than pulmonary TB. It may also affect multiple organs at the same time in the case of disseminated tuberculosis increasing the chance of death of the children who are already weakened by the HIV virus. On the other hand, this result is discordant with the study conducted in Nigeria. The

possible source of this variation could be the difference in study period as the previous study was conducted over one-year period.

Another factor that predictor mortality among TB/HIV co-infected children was ART drug adherence. The result shows that children who had fair or poor drug adherence were three times more likely to die than those with good ART drug adherence. This result is in line with a study conducted in India(24). This may be because ART drugs have role in viral suppression which decreases the viral load helping the immune system to recover. Therefore, children with good adherence have better ability to fight the co-infection. But those who have fair or poor drug adherence may end up with treatment failure speeding up the viral replication thus leading to weakened immunity and death.

MDR-TB was another predictor of mortality that was identified by this study. Individuals co-infected with MDR-TB and HIV was six times at higher risk of mortality than children co-infected with non-drug resistant TB and HIV. A study conducted in South Africa among MDR TB infected children showed that those who are HIV positive had more than two times higher mortality rate than those who were HIV negative which is in line with the result of this study(44). The reason for this can be, the treatment challenges that are experienced during treating the drug resistant strains that require second line regimens which have more adverse effects than the first line anti tuberculosis drugs affecting the co-infected child synergistically with the ART drugs. Moreover, as the treatment requires longer period than the non-drug resistant TB, it increases the children's risk by exposing them for longer period.

Limitations and strength of this research

Limitation of the study

Since this study was conducted based on secondary data, charts excluded due to incomplete data and lost charts which may be related to mortality might underestimate the result of the study. The poor management of charts of children who died will also negatively affect the result. On the other hand, since TB is not recorded on most of the ART registers, it makes it difficult to find charts of all TB/HIV co-infected children on the study period which also affect the outcome.

Strengths of the study

Since all TB/HIV co-infected children on the study area were included and hospitals with the highest number of patients were selected, the result is representative and can be generalized to the respective population. In addition, given that the study was conducted for ten years period it could help to see the long-term effect of the anti-retroviral drugs. Moreover, because it includes both pre-ART and ART periods, it helps to compare the impact of the two periods.

7. Conclusion and Recommendation

Mortality rate of TB/HIV co-infected children in selected public hospitals in SNNPR, Ethiopia was high. Moreover, Anemia, drug resistant tuberculosis, extra pulmonary TB and poor adherence to ART drugs were identified as the predictors of mortality among these children. Close monitoring of those children with anemia, drug resistant TB and extra-pulmonary TB is recommended.

Recommendation

Based on the findings of this study, the following recommendations are forwarded to the respective organs.

1. To governmental and non- governmental organizations
    - ✓ Provide trainings concerning screening, diagnosis and management of TB/HIV co-infection in children to health care providers
    - ✓ Strengthen the linkage system between TB and HIV care services in the pediatrics
    - ✓ Provide updated modules regarding screening, diagnosis and management of TB/HIV co-infection to health facilities
2. To health care providers
    - ✓ Due to high vulnerability of children with extra pulmonary TB, drug resistant TB and anemia, it is recommended to give special attention to them.
    - ✓ It is better if ART adherence team should act actively towards counseling caregivers about the importance of adhering to the drugs
    - ✓ The children must be screened for drug resistant and extra pulmonary TB
    - ✓ Parents or caregiver must be aware of TB prevention
3. To researchers
    - ✓ Prospective cohort study on predictors of mortality among TB/HIV co-infected children in order to fill the gap of incomplete data
4. To parents or caregivers
    - ✓ Children should not skip any appointments for their follow up in order to not miss any package of care in the ART clinic
    - ✓ Children should be strictly followed when it comes to taking ART drugs so that they won’t miss a dose and adhere to the prescribed drugs

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ANNEX

Annex I Information Sheet

Title of the study: Survival and Predictors of mortality among TB-HIV co-infected children attending ART clinics of selected public hospitals in SNNPR, Ethiopia, 2020

Name of Investigator: Jifare Gemechu (BSc.)

Name of the Organization: AAU

Name of the Sponsor: AAU

Introduction; This information sheet is prepared for……hospital and HIV care clinic coordinating offices of Hossana town. The aim of the form is to make purpose of research, data collection procedures clear to the above concerned offices and get permission to conduct the research.

Purpose of the Research Project: To determine the incidence and predictors of mortality among TB/HIV co-infected children attending ART clinic of ……..hospital.

Procedure: In order to conduct the study and achieve the above objective, necessary information will be obtained from follow up forms in the medical charts of TB/HIV infected children attending ART clinic.

Risk and/or Discomfort: Since the information needed will be obtained from the medical charts, it will not cause any harm to the participant. Any identification of the participant including the name will not be recorded on the questionnaire. And all information obtained from the charts will be kept secretly. Moreover, the information will only be used for the purpose of the study.

Benefit: The study will not have direct benefit for the participants. But identifying the predictors will help program planers to plan accordingly and improve prevention and treatment services which benefit the study participants and other clients in the program. Most of all, the result of this study has direct benefit for health planners and managers especially for those on HIV and TB prevention, treatment and support program planning and management.

Confidentiality: To assure the confidentiality of the information, data was collected by those who work on ART clinics without the name of the participants. The information obtained from this study was only be revealed to principal investigator and was stored in a computer locked by password.

Person to contact: the following contact addresses were given to contact investigators at any time

Jifare Gemechu, AAU University, College of Health Sciences, Department of Child health and pediatric Nursing: principal investigator

Phone: 0912458932

Email: jifareg@gmail.com

Annex II Questionnaire

Date of data collection: / / /DD/MM/YY

Name of the facility: _____

Name of the data collector: _____Signature_____

Name of the supervisor: _____Signature_____

Code: _____

Address: _____

No	**Part I: Socio demographic characteristics**		
	Child socio demographic characteristics		
101	Date of enrolment	/ / /DD/MM/YY	
102	Age at enrolment	Months/ year	
103	Sex	1. Male 2. Female	
104	Birth order	_____	
105	Mother HIV status	1. Positive 2, Negative 3. Unknown	
106	Child lives with	1. Parent 2. Guardian 3, Orphan 4. Others	
	Care giver socio demographic characteristics		
107	Age	_____	
108	Sex	1. Male 2. Female	
109	Relationship to the child	1. Mother 2. Father 3. Step parents 4. Sibling 5. Others (specify)_____	
110	Address	1. Urban 2. Rural 3. Not recorded	
111	HIV status of care giver	1. Positive 2, Negative 3. Unknown If 2 or3 skip to 14	
112	If positive, is he/she in HIV care?	1. Yes 2. No	
	Part II: base line clinical characteristic		
201	WHO clinical stage	1. I 2. II 3. III 4. IV	

202	CD4+ count/percent	_____(_____%)	
203	Hgb level	_____mg/dl	
204	Height/length at baseline	(----------) cm	
205	History of OI	1. No 2. BP 3. PTB 4 EPTB 5. TO 6. TE 7 Ulcer 8. DC/DA 9. PCV 10 CT 11. CM 12. NHL 13. KS 14. CCa 15. Z. 16. Others	
	Part III: HIV care/ ART follow up		
301	Date confirmed HIV+	/ / (DD/MM/YY)	
302	ART Eligible date	/ / (DD/MM/YY)	
303	Eligibilitye criteria	1. CD4 cell count 2. WHO clinical stage 3. Both 3.Test and treat4. Not recorded	
304	Date ART started	/ / (DD/MM/YY)	
305	Initial Regimen	_____	
306	Was the Regimen change	1. Yes 2. No	If 2 go to 28
307	When was it changed	/ / (DD/MM/YY)	
308	New regimen		
309	Reason for regimen change	1. Side effects 2. Treatment failure 3. TB 4. Stock out 5. Others	
310	Did the child had treatment failure	1. Yes 2. No	
311	If yes when?	_____	
312	Type of failure	1. Immunologic 2, virologic 3. Clinical	
313	Second line regiment	1. _____	
314	OI prophylaxis	1. Not given 2. Co-trimoxazole 3. INH 4.	

		Fluconazole 5. Others specify----------	
315	Adherence within 3 month of ART initiation	1. Good 2. Fair 3. Poor	
	Part IV: Tuberculosis related questions		
401	Time of TB occurrence	1. Pre ART 2. ART	
402	Site of TB infection	1. Pulmonary 2. Extra pulmonary	
403	WHO stage at TB diagnosis	1. III 2. IV	
404	CD4+ cells	_____(_____%)	
405	Hemoglobin at TB diagnosis	_____	
406 407	Drug resistance Previous history of TB	1. No 2. MDR 3. XDR 1. Yes 2. No	

Parts IV follow up form to be filled

Follow up date	Months on ART	Current status					Weight (kg)	WHO stage	TB status	INH	CPT	ART Adh. (G,F,P	CD4	Hgb (g/d)	OIs
		Alive	Dead	Loss to follow up	Transfer out	stop									

If the patient Dead, drop out, transfer out or stop when was it occurs -------/------/-----
DD/MM/YY?

501	Final status	1. Death 2. Alive 3. Transfer out 4. Loss to follow-up	
502	Final status date from enrolment (in month	_____	
503	Final status date from TB diagnosis (in months	_____	
504	Periods at which the final status occurred	1. Pre ART 2. ART	

Annex: III Training module for data collectors and supervisors

I.Instruction

- ☞ Identify target charts to be reviewed
- ☞ Procedures to be followed during review of charts
- ☞ When to start data collection and when to end

II. Methods of training

- ✓ Pass through the instrument or data collection tool with data collectors to point out specific instructions
- ✓ Provide an example of a completed instrument or an interview transcript for the data collectors
- ✓ Allow data collectors to practice with the tool

Table: training module manual

Data collection methodOr instruction	Data collector	Training needs	Training activities
Data extraction from selected charts by using the tool	BSc Nurses Diploma Nurse	Data extraction techniques How to follow and fill the instrument	Observation instruction Trainee observation practice