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ORIGINAL RESEARCH

Incidence of Pneumonia and Predictors Among Human Immunodeficiency Virus Infected Children at Public Health Institutions in the Northwest Part of Ethiopia: Multicenter Retrospective Follow-Up Study

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Introduction: Pneumonia is an inflammation of the lung parenchymal structure secondary to hematogens spread of pathogens, inhalation, or aspiration. It is also one of the most frequently occurring opportunistic infections in HIV-infected children. In Ethiopia, data on the incidence and predictors of opportunistic infection, especially pneumonia, among HIV-infected children is very limited. Hence, this study aimed to assess the incidence of pneumonia and predictors among HIV-infected children at public health institutions in the Northwest part of Ethiopia.

Methods: An institution-based retrospective cohort study was conducted among 342 HIV-infected children at public health institutions from January 1, 2013 to December 30, 2020. Log rank test was used to compare the survival curves between different explanatory variables. Bivariable Cox proportional hazards regression model was employed for each explanatory variable to check the association with the outcome variable. Variables found to have a p-value of < 0.25 in the bivariable analysis were candidates for the multi-variable proportional hazard model. Cox proportional hazards model was used at 5% level of significance to identify predictors of pneumonia.

Results: This study included 342 records of HIV-infected children who started antiretroviral therapy between the periods of January 1, 2013 to December 30, 2020. The overall incidence rate of pneumonia during the follow-up time was 5.57 (95% CI: 4.4, 7.0) per 100 child-years of observation. Those children who did not take cotrimoxazole preventive therapy (AHR: 3, 95% CI: 1.40, 6.44), being underweight at baseline (AHR: 2.6, 95% CI: 1.41, 4.86), having baseline advanced disease (clinical stages III and IV) (AHR: 2.8, 95% CI: 1.30, 6.04), and presenting with recently detected viral load (AHR: 5.9, 95% CI: 2.53, 14.06), were more likely to develop pneumonia.

Conclusion: Pneumonia incidence rate was high. Providing prophylaxis and nutritional supplementation for those children with baseline advanced disease stage, low weight for age and detectable viral load would reduce pneumonia occurrence.

Keywords: pneumonia, incidence, HIV, children, Ethiopia

Background

Pneumonia is one of the most frequently occurring opportunistic infections in human immunodeficiency virus (HIV) infected children. Bacterial respiratory tract infections occur more frequently in HIV-positive children and HIV-exposed infant than in HIV-negative children.[1] Pneumonia continues to be the leading cause of morbidity and mortality in children worldwide.[2] In 2017, pneumonia caused an estimated 6.3 million deaths globally; 1 million of these occurred in 5 to 14 year old children.[3] Globally,

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1.4 million episodes of clinical pneumonia were attributable to HIV in 2015.[4] In 2010, 88,000 pneumonia deaths occurred in HIV-infected children, and 93% of deaths were among children under 5 years of age in Africa.[5] Acute and chronic respiratory illnesses are the most common presenting complaint of morbidity in HIV-infected children.[6] HIV-infected children are 6.5 times more at risk of hospitalization and at higher risk of death from pneumonia when compared to HIV-uninfected children, especially in African countries.[7] In the highest HIV burden countries in sub-Saharan Africa, 60% of pneumonia deaths occur in HIV-infected children.[5,8] The proportionate contribution of sub-Saharan Africa to the global estimates of pneumonia among HIV-infected children was 72%.[4] HIV-infected children carry a high burden of lower respiratory zone infection usually caused by viruses, bacteria, and mycobacterium tuberculosis. Bacteria are an important cause of childhood pneumonia. Haemophilus influenzae type b and Streptococcus pneumonia are the most common causes and vaccines against them have been introduced to reduce the mortality from childhood pneumonia.[9] Streptococcus pneumonia is part of normal flora in the upper part of the respiratory system but it can cause severe invasive diseases like meningitis, septicemia, and pneumonia.[10] Pneumocystis pneumonia was one of the most frequent opportunistic infections before the widespread use of antiretroviral drugs and effective prevention of mother-to-child transmission. It commonly occurs when a patient's immunity is significantly suppressed.[11]

As evidence shows from study in Ethiopia, pneumonia is one of the leading opportunistic infections that predict nearly 60% of hospitalizations among HIV-infected children in the six months following antiretroviral therapy (ART) initiation.[12] A study in the United States revealed that there were 87 community acquired pneumonia (CAP) episodes among HIV-infected children, with an incidence of 3.32 cases per 100 PY of follow-up.[13] Another study, in Latin America, showed that the incidence of overall opportunistic infection among HIV-infected children was 23.5 per 100 PY; of these, the overall incidence of pneumonia was 8.1 per 100 person years.[14]

Evidence from other studies shows that young age, malnutrition, low immunity, smoking or air pollution exposure, high viral load and low hemoglobin level are risk factors for pneumonia among HIV-infected patients.[11,15,16] Although sufficient studies are done about pneumonia among children, there is a scarcity of information on children infected with HIV, especially in sub-Saharan Africa where the HIV burden is high.[17] Even though pneumonia was the first common opportunistic infection among HIV-infected children in Ethiopia,[18] data on the incidence and predictors of pneumonia among HIV-infected children is very limited.

Therefore, this study is intended to fill this information gap. Moreover, for better intervention and treatment, up-to-date information regarding the occurrence of pneumonia among HIV-infected children is important. So, the aim of this study is to assess the incidence of pneumonia and predictors among HIV-infected children at public health institutions in the northwest parts of Ethiopia. The results of this study provide evidence-based information for decision makers, health care workers, and researchers to develop general or specific effective preventive strategies and programs to reduce the burden of pneumonia in HIV-infected children.

Methods

Study Design, Setting and Period

An institution-based retrospective cohort study was conducted at public health institutions in the northwest parts of Ethiopia from January 1, 2013 to December 30, 2020. Bahir Dar city was the selected study area; it is the capital city of Amhara regional state, located in the northwest of Ethiopia. It is found 565 km away from Addis Ababa, the capital city of Ethiopia. According to the Bahir Dar city administration report, estimated total population in 2020 was 389,177, of which 183,984 were male and 205,193 were female. Additionally, the estimated number of children under 15 years of age is 147,983. Currently, the total number of pediatric population on ART at public health facilities in Bahir Dar city is 763. The city has two referral hospitals, one primary hospital, and ten health centers, of which only one health center does not provide ART service.

Study Participants

The source population for this study was all HIV-infected children age < 15 years who started ART enrollment at public health institutions in Bahir Dar city. The study population included all HIV-infected children who started ART follow-up at public health institutions from January 1, 2013 to December 30, 2020.

Eligibility Criteria

All HIV-infected children aged less than 15 years who started ART follow-up from January 1, 2013 to December 30, 2020 were included in this study. But all HIV-infected children with incomplete baseline records such as CD4 cell count, WHO clinical stage and the first date of occurrence of event as well as transfer in from other facilities and having pneumonia at the time of ART initiation were excluded.

Sample Size Determination and Sampling Procedures

To determine the required sample size, the authors considered both objectives to calculate the largest sample size needed. For the first objective, the single-population proportion formula was used to calculate the sample size by considering the estimated incidence proportion of pneumonia among HIV-infected children taken from a study done in Debre Markos referral hospital (30%),[18] which yielded 356. For the second objective of this study, sample size was determined using double population proportion formula considering predictor variables (CD4 count, ART adherence, WHO clinical stage, past OI prophylaxis) from a study conducted at Debre Markos referral hospital.[18] By using Epi info version 7.2.4.0 statistical calculator computer software assuming 95% confidence interval, power of 80% and one-to-one ratio of exposed and unexposed group and gave the maximum sample size of 92. Therefore, 356 from the first objective was considered as the final sample size for this study. After identifying the list of 530 pediatric population who started ART at public health facilities in Bahir Dar city from January 1, 2013 to December 30, 2020, all their medical registration numbers were extracted from SMART care of the selected health institutions and a sampling frame was constructed. Finally, study unit from the frame was selected by simple random sampling using a computer generated system.

Study Variables

The dependent variable was incidence of pneumonia and independent variables were baseline sociodemographic predictors (age, sex, residence, family size, the live status of the parents, and occupation of the parent or caregiver), baseline clinical and laboratory-related predictors (functional status, developmental status, weight for age, BMI for age, weight for height, height for age, WHO clinical stage, CD4 count or %, recent viral load, and Hgb level), and treatment-related predictors (history of CPT, ART adherence, immunization status, and treatment failure).

Operational Definition

Events

Pneumonia cases were identified based on EFMOH guidelines for pediatric HIV/AIDS care and treatment.

Censored

Lost, transferred out, dropped out, died due to another cause, and completed the follow-up time before the occurrence of an event.

According to this study, pneumonia was defined as at least two of the following signs and symptoms with or without chest x-ray confirmation.

Bacterial Pneumonia

Chest in-drawing, tachypnea, grunting and presence of danger signs in young children. In older children: sudden onset of cough, sputum production, chest pain, fever and/or shortness of breath. History of acute symptoms presented over days to a few weeks and consolidation in the affected lung or lungs.[19]

Pneumocystis Pneumonia

In infants 2 to 6 months: abrupt onset of fever, tachypnea, dyspnea and cyanosis. In older children: insidious onset of low grade fever, dry cough, dyspnea exacerbated by exertion, tachypnea, tachycardia and scattered rales in the lungs. Typical chest x-ray findings revealing a perihilar interstitial infiltration with tendency to spread outwards.[19]

Level of ART Adherence

Adherence can be classified according to the percentage calculated from the number of missed pills out of the supplied pills as good, fair, and poor.

Good (≥ 95% adherence) or ≤ 3 missed pills out of 60 pills supply. Fair (85–94% adherence) or between 4 and 8 missed pills out of 60 pills supply. Poor (< 85% adherence) or ≥ 9 missed pills out of 60 pills supply.[20]

CD4 Cell Count or % Below the Threshold

CD4 cell count < 1500/mm^3 or 25% for children aged under 12 months, CD4 cell count < 750/ mm^3 or 20% for children aged 12 to 35 months, CD4 cell count < 350/mm^3 or 15% for children aged 36 to 59 months, and CD4 cell count < 200/ mm^3 or 15% for children aged ≥ 60 months, respectively.[21]

Underweight

According to WHO curve, weight for age Z score <-2 standard deviation.

Data Collection Tools and Procedures

The data collection tool was based on the Federal Ministry of Health's ART follow-up and intake form, which is currently in use at ART clinics of Ethiopian hospitals. First, the appropriate data extraction format was prepared in an English version. The data extraction form included sociodemographic characteristics, treatment, clinical, laboratory-related characteristics, and outcome-related information. The children's chart was retrieved from the chart room after having their MRN from the electronic database. The occurrence of pneumonia was ascertained by reviewing health professionals' diagnoses or reporting on the patient's chart. Any laboratory results and other clinical-related tests done at the time of ART initiation were taken as a baseline.

Data Quality Control

One day training was given to data collectors and a supervisor before the actual data collection period. A pretest was performed on 5% of the sample size one week before the actual data collection time at Felege Hiwot Comprehensive Specialized Hospital. Based on pretest experience,the variables that do not present were avoided. The data were collected by three Bsc nurses. One health officer who has experience in HIV care and follow-up was recruited to continuously supervise the data collectors. Additionally, the data were checked for completeness and consistency by the principal investigator.

Data Processing and Analysis

After the completeness and consistency were checked, the collected data were coded and entered into EPI data version 4.6. Next, they were exported to STATA version 14 for analysis. The assumption of the Cox proportional hazard regression model was checked by running a global test based on the scaled Schoenfeld residuals test. Model goodness of fit was also checked by the Cox–Snell residual test. Multi-collinearity was computed using variance inflation factor and correlation coefficient. Descriptive statistics were computed as frequency, percentage, and median and results were displayed using tables and graphs. Outcomes of each participant were dichotomized into censored or pneumonia and incidence rate was calculated for the entire period. The pneumonia-free survival time was estimated by using the Kaplan–Meier (KM) survival curve. Pneumonia-free survival time between different categorical variables was compared using KM plot and log rank test. The bivariable Cox PH model was employed to check variables that have P-value < 0.25. Then, variables with this value were selected for multivariable Cox PH regression model. Hazard ratio with a 95% confidence interval and p-value < 0.05 was used to measure association and to consider statistically significant predictors of pneumonia. WHO Anthro and Anthroplus software programs were used to assess nutritional status of the participants.

Missing data analysis for some variables was computed. After the pattern of missing data was checked and Little's test was done, missing mechanism of data was identified. Next, by using multiple imputations the data were imputed and pooled into a new complete dataset.

Results

Baseline Sociodemographic Characteristics of the Child and Parents or Child's Caregiver Information

In this study, among HIV-infected children on ART from January 1, 2013 to December 30, 2020, a total of 356 medical records of children were retrieved. Of these, 14 charts were excluded due to the exclusion criteria and the remaining 342 charts of the children were included in this study. Among those children, slightly more than half (51.46%) of the children were male. Majority (40.35%) of the children were in the age group of 5 to 9 years. The median age of the participants at the ART initiation was 8 years (IQR=5, 11). The highest proportion of pneumonia (10.23%) was seen among the 10 to 14 year age group and among children living in urban areas (17.25%) (Table 1).

Baseline Clinical and Laboratory Related Information

The majority (71.35%) and 80.12% of children were classified as normal weight and CD4 cell count above the threshold, respectively. The incidence rates of pneumonia among children categorized as underweight, WHO clinical stages III and IV, and detected viral load were 13.88, 15.65, and 17.48 per 100 PY of observation, respectively (Table 2).

Treatment Related Information

The highest proportion (81.87%) of the children had no treatment failure during the follow-up period. Children who did not receive co-trimoxazole preventive therapy had an incidence rate of 21.81 cases per 100 PY of observation (Table 3).

Incidence of Pneumonia During Follow-Up

The study participants were followed for a minimum of 0.96 months and a maximum of 86.3 months. The total person month of the cohort was 15,300.067 child-months of observation and the total person year of the cohort was also 1256.679 child-years of observation. From 342 study participants, 70 (20.47%) developed pneumonia and the remaining 272 (79.5%) were censored observation. Of these, 60 (85.71%) pneumonia cases were bacterial pneumonia and the remaining were pneumocystis pneumonia.

From all participants followed, about 59.9%, 3.8% and 14.6% were alive beyond the study period, deceased and transferred out, respectively (Figure 1). This study found that the incidence of pneumonia among HIV-infected children was 5.57 (95% CI: 4.4, 7.0) per 100 child-years of observation. As this study indicated, the incidence of pneumonia among HIV-infected children within the first year was 8.5 (95% CI: 5.8, 12.4) per 100 child-years of observation.

The overall pneumonia-free probability among HIV-infected children remained 68% (95% CI: 54.4, 78) and survival was above the median (Figure 2).

Predictors of Pneumonia Among HIV-Infected Children on ART

The Cox proportional hazard model was used to identify predictors of pneumonia among HIV-infected children. In bivariable Cox regression, sex of the child, family number, level of ART adherence, history of cotrimoxazole preventive therapy, immunization, WHO clinical stage, CD4 cell count, weight for age, height for age, hemoglobin level, treatment failure, recent viral load, and live status of the parents were variables eligible for multivariable Cox regression at p-value < 0.25. In multivariable analysis, history of cotrimoxazole preventive therapy, baseline WHO clinical stage, baseline weight for age, and recent viral load were found to be significant predictors of pneumonia among HIV-infected children. This study found that HIV-infected children who did not take cotrimoxazole preventive therapy during follow-up were 3 times (AHR: 3, 95% CI: 1.40, 6.44) more likely to develop pneumonia than those children who took cotrimoxazole preventive therapy. Children presenting with WHO clinical stages III and IV were nearly 3 times (AHR: 2.8, 95% CI: 1.30, 6.04) more likely to develop pneumonia as compared to those children with stages I and II. The risk of developing pneumonia among children who started ART underweight was 2.5 times (AHR: 2.6, 95% CI: 1.41, 4.86) higher as compared to those children who started ART with normal weight. This study also found that the hazard of developing

Table 1 Baseline Sociodemographic Characteristics of HIV-Infected Children at Public Health Institutions in Bahir Dar City, Northwest Ethiopia from January 1, 2013 to December 30, 2020 (n=342)

Variables	Categories	Outcome		IR per 100 PY
		Pneumonia (%)	Censored (%)	
Sex	Male	41(11.99)	135(39.47)	6.39
	Female	29(8.48)	137(40.06)	4.71
Child's age	2mon <5yr	17(4.75)	63(18.42)	6.83
	5–9yr	18(5.26)	120(35.09)	3.33
	10–14yr	35(10.23)	89(26.02)	7.56
Residence	Urban	59(17.25)	217(63.45)	5.84
	Rural	11(3.22)	55(16.08)	4.45
Family number	1–3	29(8.48)	169(49.42)	4.07
	4–9	41(11.99)	103(30.12)	7.51
Live status of the parents	Both alive	43(12.57)	193(56.43)	4.76
	One or both deceased	27(7.89)	79(23.10)	7.61
Occupational status	Government employed	24(18.9)	103(81.1)	5.02
	Merchant	16(18.4)	71(81.6)	5.26
	Farmer	11(25)	33(75)	6.92
	Daily laborer	12(30)	28(70)	8.68
	Housewife	7(16)	37(84)	3.93

Abbreviations: HIV, Human Immune Deficiency Virus; IR, Incidence Rate; PY, Person-Year; CI, Confidence Interval; yr, year.

pneumonia among children with detected viral load was about 6 times (AHR: 5.9, 95% CI: 2.53, 14.06) higher as compared to those children with recent undetected viral load (Table 4).

Discussion

This retrospective cohort study was conducted to assess the incidence and predictors of pneumonia among HIV-infected children who started ART at public health institutions in Bahir Dar city. This study showed that the proportion of pneumonia among HIV-infected children who started ART at public health institutions in Bar Dar City was 20.47% (95% CI: 16.5, 25). This finding was lower than the study conducted in Debre-Markos referral hospital that revealed the proportion of pneumonia was 30%.[18] The difference might be due to the previous study's length of follow-up period, which was 14 years, single study setting and sample size difference. As this study revealed, bacterial pneumonia is higher proportion than pneumocystis pneumonia, which is in agreement with the study conducted in India.[22] This is perhaps because bacterial pneumonia is the most frequent opportunistic infection due to lower immunity in HIV-patients and increased bacteria in the blood. In addition to this, the incidence of pneumocystis pneumonia has declined with the wide use of combined antiretroviral therapy and prophylaxis. The declined incidence of PCP might be also due to limited diagnostic options.

The overall incidence of pneumonia among HIV-infected children in this study was 5.57 per 100 child-years of observation, which was consistent with the study done in Northern India[23] but higher than the studies from the United States (3.32 per 100 person-years)[13] and Europe (0.54 per 100 person-years).[24] The possible explanations for this difference might be due to developed countries having more advanced technologies for diagnosis, prevention, and

Table 2 Baseline Clinical and Laboratory Related Information of HIV-Infected Children at Public Health Institutions in Bahir Dar City, Northwest Ethiopia from January 1, 2013 to December 30, 2020 (n=342)

Variables	Categories	Outcome		IR per 100 PY
		Pneumonia (%)	Censored (%)	
W/A	Normal	31(9.06)	213(62.28)	3.17
	Underweight	39(11.40)	59(17.25)	13.88
H/A	Normal	32(9.36)	196(57.31)	3.51
	Stunting	38(11.11)	76(22.22)	10.98
W/H/L (n=80)	Normal	6(7.50)	53(66.25)	3.07
	Wasting	11(13.75)	10(12.50)	20.61
Functional status (n=263)	Working	44(16.75)	200(76.05)	4.66
	Ambulatory	9(3.42)	8(3.04)	16.13
	Bedridden	0(0.00)	2(0.76)	0
Developmental status (n=79)	Appropriate	12(15.19)	50(63.29)	5.66
	Delayed	4(5.06)	11(13.92)	13.17
	Regressed	1(1.27)	1(1.27)	29.5
WHO clinical stage	Stage I & II	13(3.80)	203(59.35)	1.45
	Stage III & IV	57(16.66)	69(20.17)	15.65
CD4 cell count (cells/mm^3)	Above the threshold	48(14.04)	226(66.08)	4.44
	Below the threshold	22(6.43)	46(13.45)	12.51
Hgb level (g/dl)	11–19	31(9.06)	257(75.15)	2.69
	6–11	39(11.40)	15(4.39)	36.93
Recent viral load	Undetected VL (≤150copies/mL)	9(2.63)	215(62.87)	0.99
	Detected VL (>150copies/mL)	61(17.84)	57(16.67)	17.48

Abbreviations: HIV, Human Immune Deficiency Virus; W/A, Weight for Age; H/A, Height for Age; W/H/L, Weight for height/Length; CD4, Cluster of Differentiation 4; IR, Incidence Rate; PY, Person-Year; CI, Confidence Interval; WHO, World Health Organization; g/dl, gram per deciliter.

management of infections than developing countries. However, this finding is lower than the studies conducted in Spain (13.7 per 100 child-years)[25] and Latin America (8.1 per 100 person-years).[14] The reason for variation with the study in Spain might be due to study population difference since it included HIV-infected children less than 17 years of age and the study included a arger sample size (1307) than the current study. The difference with the study in Latin America might be due to the time period of the study and the longitudinal behavior of the study. Moreover, the current well-organized HIV prevention, treatment and care for HIV-infected children might make a difference. According to this study the incidence of pneumonia among HIV-infected children was higher within the first year of ART initiation, which was in-line with the study done in Uganda,[26] in resource-limited settings,[27] and in Asia.[28] This may be due to the fact that patients have low immunity and low awareness about adherence to HAART at ART initiation time.

This study found that the risk of developing pneumonia among HIV-infected children who took cotrimoxazole preventive therapy prophylaxis was low as compared to those HIV-infected children who did not take CPT. Retrospective study in Ethiopia indicated that cotrimoxazole preventive therapy is a feasible, cost-effective, and safe way of using

Table 3 Treatment-Related Information of HIV-Infected Children at Public Health Institutions in Bahir Dar City, Northwest Ethiopia from January 1, 2013 to December 30, 2020 (n=342)

Variables	Categories	Outcome		IR per 100 PY
		Pneumonia (%)	Censored (%)	
History of CPT	Yes	20(5.85)	235(68.71)	1.94
	No	50(14.62)	37(10.82)	21.81
Immunization status	Completely immunized	19(5.56)	217(63.45)	2.0
	Partially immunized	37(10.82)	42(12.28)	16.52
	Not immunized	14(4.09)	13(3.80)	16.51
Level of ART adherence	Good	50(14.62)	252(73.68)	4.30
	Fair/poor	20(5.84)	20(5.84)	20.91
Treatment failure	No	29(8.48)	251(73.39)	2.66
	Yes	41(11.99)	21(16.14)	24.09

Abbreviations: ART, Antiretroviral Therapy; CPT, Cotrimoxazole Preventive Therapy; HIV, Human Immune Deficiency Virus; IR, Incidence Rate; PY, Person-Year; CI, Confidence Interval.

cotrimoxazole to reduce the incidence of opportunistic infections.[29] Another prospective study, conducted in South Africa, revealed that CPT reduces HIV-related morbidity and hospitalization not only by preventing pneumocystis pneumonia but also reducing the incidence of bacterial infection.[30] According to Ethiopian ART guideline, early initiation of CPT for HIV-infected children is recommended to prevent pneumocystis pneumonia, bacterial infections, toxoplasmosis gondii and protozoal infections.[31]

As the current study indicated, children who started ART with the baseline WHO stages III and IV were more likely to develop pneumonia as compared to those children who started ART with the baseline WHO clinical stages I and II. This was similar to the studies done in Asia[28] and India.[23] Another similar study also observed in Nigeria showed that advanced baseline WHO clinical stage is an independent risk factor for the occurrence of infections.[32] This could be because of lower immunity with advanced WHO staging which increases the occurrence and recurrence of opportunistic

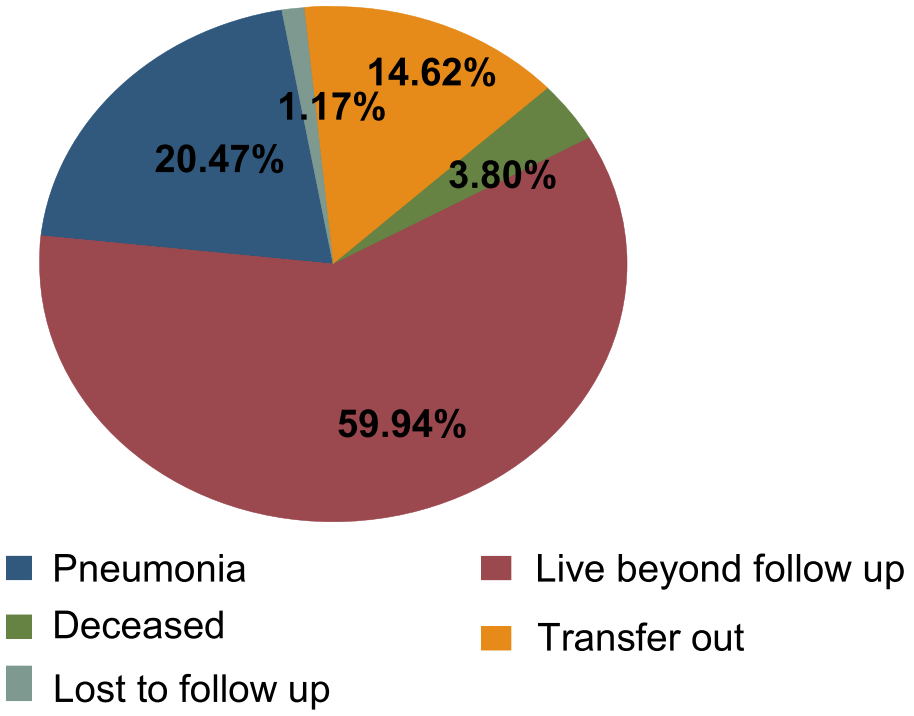

Figure 1 Outcome status of HIV-infected children at public health institutions in Bahir Dar city, Northwest Ethiopia from January 1, 2013 to December 30, 2020 (n=342).

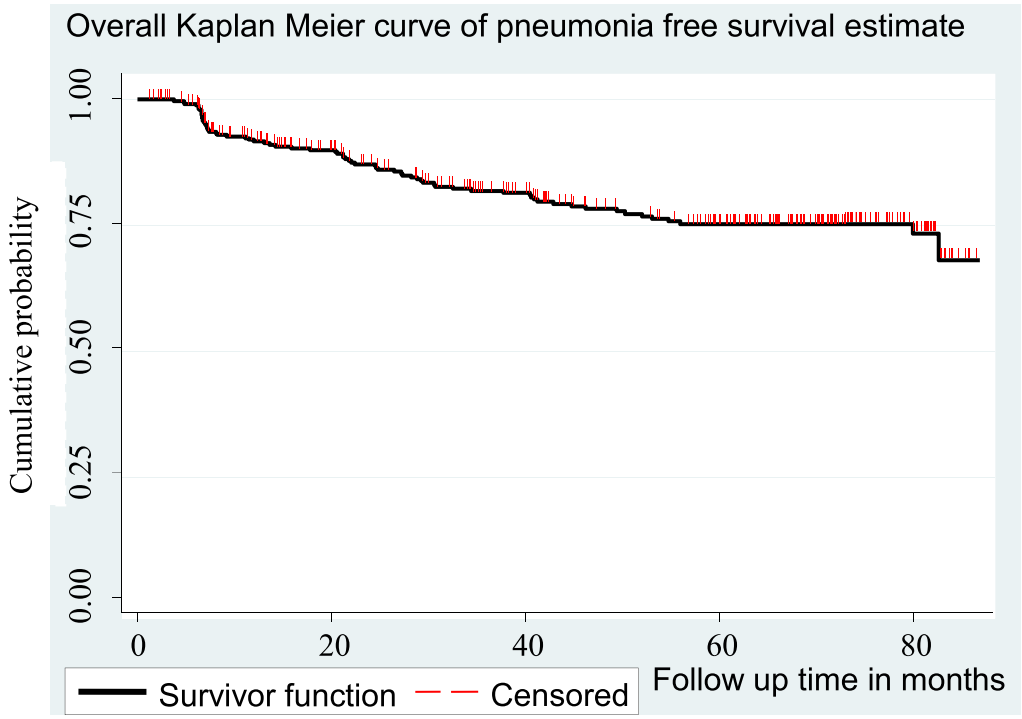

Figure 2 Overall Kaplan–Meier curve of pneumonia-free survival probability of HIV-infected children at public health institutions in Bahir Dar city, from January 1, 2013 to December 30, 2020 (n=342).

infections.[33] This is explained by as the immune status of the patient living with HIV infection becomes weaker, the HIV clinical stage gets higher.[34] Therefore, stage I and II patients have stronger immunity than stage III and IV patients who have moderate and severe opportunistic infections, respectively.

This study also found that the risk of developing pneumonia among HIV-infected children who started ART underweight was higher as compared to those HIV-infected children who started ART with normal weight. This finding is supported by studies done in Kenya,[35] Uganda,[36] and in Asia.[28] This could be due to the fact that malnutrition is the major cause of immune deficiency. It elicits dysfunctions in the immune system and promotes increased vulnerability of the host to infections.[37] In other words, it might be due to the fact that infection also contributes to malnutrition due to appetite loss, which leads to inadequate dietary intake resulting in weight loss, lowered immunity, mucosal damage, invasion by pathogens and impaired growth and development in children.

Moreover, the hazard of developing pneumonia among children with detected viral load was much higher as compared to children with undetected viral load. This was similar to the studies done in Denmark[38] and the United States.[13] The study in Brazil has shown that detectable viral load doubled the risk of pneumonia among HIV-infected children (AHR: 2.2).[16] This could be explained by the fact that the higher the viral load, then the faster the CD4 cell count will fall, resulting in the greater risk of infections.[39]

A surprising result of this study was the absence of significant association between CD4 cell count and pneumonia. This finding is consistent with the study conducted in Indonesia.[40] In contrast to this, various studies have shown worse disease severity and an increased frequency of opportunistic infections when CD4 cell levels are below the threshold.[41,42] This discrepancy might be attributable to the presence of high levels of sustained adherence to HAART necessary to improve the immunological and clinical outcomes of the HIV-infected children.

Therefore, this study implies that even though the government strives to ensure healthy lives and promote well-being of all HIV-infected patients by preventing, diagnosing, and treating opportunistic infections, pneumonia remains to be a cause of morbidity among HIV-infected children.

Table 4 Bivariable and Multivariable Cox Regression Analysis of Predictors of Pneumonia Among HIV-Infected Children at Public Health Institutions in Bahir Dar City, Northwest Ethiopia from January 1, 2013 to December 30, 2020 (n=342)

Variable	Category	CHR (95% CI)	AHR (95% CI)	P-value
Sex	Male	1.34 (0.83, 2.26)	1.11 (0.67,1.85)	0.672
	Female	1	1	
Family number	1–3	1	1	
	4–9	1.88 (1.16, 3.02)	1.09 (0.63, 1.90)	0.747
Level of adherence	Good	1	1	
	Fair/Poor	4.23 (2.51, 7.12)	0.96 (0.51, 1.82)	0.912
Cotrimoxazole	Yes	1	1	
	No	10.15 (6.02, 17.12)	3.01 (1.40, 6.44)	0.004
Immunization status	Completely immunized	1	1	
	Partially immunized	7.63 (4.38, 13.30)	1.55 (0.70, 3.44)	0.277
	Not immunized	7.61 (3.8, 15.2)	1.85 (0.73, 4.71)	0.193
WHO clinical stage	Stage I & II	1	1	
	Stage III & IV	10.14 (5.54, 18.55)	2.80 (1.30, 6.04)	0.008
CD4 cell count	Above the threshold	1	1	
	Below the threshold	2.62 (1.58, 4.36)	1.24 (0.68, 2.25)	0.465
W/A	Normal	1	1	
	Underweight	4.09 (2.55, 6.57)	2.62 (1.41, 4.86)	0.002
H/A	Normal	1	1	
	Stunted	2.98 (1.86, 4.77)	0.82 (0.45, 1.51)	0.536
Hgb level(g/dl)	11–19	1	1	
	6–11	12.50 (7.70, 20.29)	1.05 (0.50, 2.16)	0.895
Treatment failure	No	1	1	
	Yes	8.30 (5.13, 13.40)	1.15 (0.61, 2.15)	0.659
Recent viral load	Undetectable	1	1	
	Detectable	16.81 (8.34, 33.90)	5.96 (2.53, 14.06)	0.000
Live status of the parent	Both alive	1	1	
	One or both deceased	1.53 (0.94, 2.48)	0.75 (0.43, 1.31)	0.325

Abbreviations: CD4, Cluster of Differentiation 4; HIV, Human Immune Deficiency Virus; CHR, Crude Hazard Ratio; AHR, Adjusted Hazard Ratio; CI, Confidence Interval; W/A, Weight for Age; H/A, Height for Age; WHO, World Health Organization; g/dl, gram per deciliter.

Limitation

This study is not without limitations. The data for this study was obtained from charts. Therefore, some variables could not be found such as parents' educational status, income, and cigarette smoking behavior that could be potential predictors of the event. As is common in resource-limited settings, the diagnostic options such as bacteriologic confirmation were limited, which may potentially lead to misclassification. A limited previous study done in Ethiopia makes comparison and discussions difficult in the local context.

Conclusion

This study found that among HIV-infected children who started ART at public health facilities in Bahir Dar city, two from ten children developed pneumonia during follow-up time. As this study showed, predictors such as not taking past cotrimoxazole preventive therapy, being underweight at baseline, baseline advanced WHO clinical stage (III and IV), and detected viral load were predictors of pneumonia among HIV-infected children.

Abbreviations

ART, Antiretroviral Therapy; BMI, Body Mass Index; CAP, Community Acquired Pneumonia; CMV, Cytomegalo Virus; CPT, Cotrimoxazole Preventive Therapy; EFMOH, Ethiopian Federal Ministry of Health; FU, Follow-Up; HAART, Highly Active Antiretroviral Therapy; Hgb, Hemoglobin; HIV, Human Immunodeficiency Virus; IPD, Invasive Pneumococcal

Disease; KM, Kaplan–Meier; LRTI, Lower Respiratory Tract Infection; MRN, Medical Recording Number; NGOs, Non-Governmental Organizations; OIs, Opportunistic Infections; PCP, Pneumocystis Pneumonia; PH, Proportional Hazard; PMTCT, Prevention of Mother to Child Transmission; PY, Person-Year; SARI, Severe Acute Respiratory Infection; SDG, Sustainable Development Goal; SMART, Strategies for Management of Antiretroviral Therapy.

Data Sharing Statement

Data will be available upon request from the corresponding author.

Ethical Considerations

In order to conduct this research, the authors tried to address the Declaration of Helsinki Ethical principles for medical research. First, ethical clearance was obtained from Bahir Dar University, College of Medicine and Health Sciences, school of health sciences with Ethical Review Board number (CMHS/IRB 01-008) decided on the date February 26, 2021. Then, a letter was written to each study institution in Bahir Dar city by Bahir Dar University. A supporting letter was obtained from each selected health facilities general manager, health centers head and coordinators. As this was a retrospective study, informed consent from an individual patient was not requested because the authors had no physical contact with them and the data were collected from their medical charts after their discharge from the health institutions. Information in the data extraction was anonymous. The confidentiality of the information was kept throughout the study process and the information was used only for the study purpose.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no competing interests in this work.

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