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ORIGINAL ARTICLE

Incidence of Opportunistic Infections among HIV-infected Children on ART at Gondar University Specialized Hospital, Ethiopia

Dagnaw Amare Mequanente[1], Pilavadisamy Srinivasan[2]*, G Mallika[3], Peer Mohamed Thamimul Ansari[4], Mequanent Wale[5]

1 Institute of Public Health and Biotechnology, University of Gondar, Ethiopia
2 Koneru Lakshmiah Education Foundation, Deemed to be University, Andhra Pradesh, India
3 Department of Commerce, Vyasa Arts & Science Women's College, Vasudevanallur, Tamil Nadu, India
4 Department of Hotel Management, University of Gondar, Ethiopia
5 Department of Biostatistics, University of Gondar, Ethiopia

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* **Corresponding author**.

mallivasan@gmail.com

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Abstract

Objective: To assess the prevalence and determinants of opportunistic infections among HIV-infected children receiving antiretroviral medication (ART) at the University of Gondar's comprehensive specialty hospital. **Methods:** A retrospective cohort research was undertaken at the University of Gondar comprehensive specialized hospital between January 11, 2017, and January 10, 2022. The study included 389 HIV-positive children on antiretroviral therapy. A data extraction form derived from the ART entry and follow-up forms was used to collect data from the charts of HIV-infected persons. The data was entered using Epi-dataTM Version 4.5, and the data was analyzed using StataTM Version 16. ofBivariate and multivariate semi-parametric and parametric regression models were fitted to identify risk factors of opportunistic infections. The Kaplan Meier survival curve was used to calculate the time gap between opportunistic infections. **Result:** Between January 11, 2017, and January 10, 2022, 389 HIV-infected children started antiretroviral therapy (ART). The overall Incidence of opportunistic infections was 4.2 (95 percent CI 3.75 to 4.46) per 100 person-year observation during the follow-up period, which lasted a median of 67 months (IQR=58-76 months). The most common OI at follow-up was bacterial pneumonia, which was 13.5 (95 percent CI: 10.29,17.7). Children with baseline CD4 200 cells/l counts (AHR= 2.05 (1.40, 3.00), baseline Hgb level of 10 g/dl (AHR=5.87 (3.97,8.69), ever taking IPT (AHR=1.71(0.94, 3.11), and HIV-infected children with fair/poor ART adherence (AHR=1.41(0.90, 2.19) were all significantly linked to the development of opportunistic infections. **Conclusion**: In this study, the rate of opportunistic infections among HIV-positive children was quite low. OIs were significantly associated with characteristics such as baseline CD4 count, Hgb level, adherence to ART, and use of IPT. We feel that early screening and treatment of OIs should be explored as a result of due

to the aforesaid findings above. Additionally, adherence assistance through phone calls and case managers might be increased. Furthermore, at each follow-up examination, children with severe immunodeficiency and advanced disease stages at the time of ART initiation should be closely monitored and extensively screened for the occurrence of OIs. Furthermore, at each follow-up examination, children with severe immunodeficiency and advanced disease stages at the time of ART initiation should be closely monitored and extensively screened for the occurrence of OIs. Additionally, adherence assistance through phone calls and case managers might be increased.

Keywords: Children; Antiretroviral therapy; HIV; Opportunistic infections; Ethiopia

1 Introduction

Infections with HIV/AIDS continue to be a major source of morbidity and mortality [1,2]. According to a 2018 report, 37.9 million people worldwide were living with HIV [3]. Eastern and Southern Africa are home to 54 percent of PLHIV [4]. Sub-Saharan Africa (SSA), which includes Ethiopia, is the most severely affected region, with new HIV infection rates among the top twenty-five countries [5,6]. According to 2017 study, 36.9 million people live with HIV/AIDS, with new infections down 18% since 2010 [7,8]. Nonetheless, this pace of decline is insufficient to meet the 2030 target of eradicating AIDS [9]. Only 21.7 million HIV-positive people have access to antiretroviral medication, leaving the rest at risk of HIV-related complications [10,11].

Opportunistic infections (OIs) are diseases that strike persons with weakened immune systems more frequently and severely, especially those with the weakest immune systems, such as those with PLHI [12]. Even with improved ART, opportunistic infections continue to cause morbidity and mortality in HIV-infected children [12–14].

For a variety of reasons, including poor adherence, drug toxicities, drug interactions, or the initial acquisition of a drug-resistant strain of HIV-1, some HIV-infected children do not have a sustained response to antiretroviral drugs are the associated factors of OIs for children who have HIV/AIDS [15]. As a result, despite antiretroviral therapy (ART), opportunistic infections continue to cause significant morbidity and mortality in HIV-infected children with HIV-1 infection. Opportunistic infections (OIs) are diseases that strike persons with weakened immune systems more frequently and severely, especially those with the weakest immune systems, such as those with PLHIV [4]. Even with improved ART, opportunistic infections continue to cause morbidity and mortality in HIV-infected children [5,6].

For various reasons, including poor adherence, drug toxicities, drug interactions, or the initial acquisition of a drug-resistant strain of HIV-1, some HIV-infected children do not have a sustained response to antiretroviral drugs. As a result, despite antiretroviral therapy (ART), opportunistic infections continue to cause significant morbidity and mortality in HIV-infected children with HIV-1 infection. Even though two studies on the Incidence of opportunistic infections among HIV-infected children on ART in Ethiopia have been conducted, updated information about the Incidence of opportunistic infections and its predictors is scarce in the University of Gondar comprehensive specialized hospital in northwest Ethiopia. As a result, this study looked at the prevalence of opportunistic infections in HIV-positive children taking antiretroviral therapy (ART).

2 Methodology

2.1 Study design, setting, and period

A retrospective analysis was conducted on HIV-positive HIV-infected children on HAART who attended chronic HIV care clinics at the University of Gondar comprehensive and specialized hospital in Amhara regional state, northwest Ethiopia, from January 11, 2017, and January 10, 2022. The University of Gondar's comprehensive and specialty hospital serves a population of about 5 million people in northwest Ethiopia. A range of communicable and non-communicable diseases have been documented in the catchment population. Health services units include outpatient clinics, maternity clinics, emergency wards, adult HIV-infected children, pediatric HIV-infected children, community clinics, and laboratory service. The hospital has 518 beds and sees between 350 and 400 HIV-positive children daily, with about 100-120 visiting the clinic.

2.2 Study participant

2.2.1 ***Inclusion***

All HIV-positive children (under the age of 15) who had been started on antiretroviral medication (ART) at the University of Gondar's comprehensive and specialized hospital were included in the study. At least one follow-up visit occurred between January 11, 2017, and January 10, 2022.

2.2.2 ***Exclusion***

The study eliminated HIV-positive children whose ART start dates were unclear and who were hospitalized with insufficient baseline data (CD4 count, hemoglobin level, WHO clinical stage, weight, and height).

2.3 Sampling procedures

All HIV-infected children who were ever started on antiretroviral therapy (ART) at the University of Gondar's comprehensive and specialized hospital were gathered. Data was taken from the charts of 389 HIV-infected children on antiretroviral therapy (ART). After eliminating incomplete information, 389 HIV-infected children's records matched the study's criteria and were included.

2.4 Study Variables

The dependent variable for this study was the occurrence of any opportunistic infections during follow-up. The independent variables included: Socio-demographic characteristics (age, sex, residence, religion, marital status of care giver, relationship of care giver, current status of parents, occupation of the caregiver, and family size); Clinical and laboratory predictors (i.e., WHO clinical stage, CD4 count, hemoglobin (Hgb) level, underweight, wasting, stunting, history of Prevention of Mother to Child Transmission (PMTCT), prior history of OIs, functional status, and developmental status); and ART and other medication-related predictors (i.e., past OI prophylaxis, type of baseline ART regimen, ART eligibility criteria, presence of regimen changed, level of ART adherence, ever taking Isoniazid Preventive Therapy (IPT), ART side effects, and ART treatment failure).

2.5 Operational definitions

This study considered an event when an HIV-infected child developed any form of OIs after starting ART during the follow-up period. Censored was recorded when HIV-infected children dropped or transferred out (dead or alive) to other health institutions or are still on active ART follow-up but had not developed any OIs by the end of the study[13,16]. According to the percentage of drug dosage calculated from the total monthly dose of ART drugs, adherence was classified as good, fair, or poor. Good was defined as compliance equal to or greater than 95 percent or three missed doses per month; fair as 85–94 percent compliance and between 4 and 8 missed doses per month; and poor as less than 85 percent compliance or nine missed doses per month.

2.6 Procedures for data collection and quality assurance

The data extraction form was based on the federal Ministry of Health's HIV-care/ART follow-up and intake forms, used in Ethiopian hospitals' ART clinics. The data extraction form included the following variables: socio-demographic characteristics, ART and other medication, clinical, and laboratory-related information. Data were collected by two BSc-prepared nurses working in the ART clinic of the University of Gondar comprehensive specialized hospital. To ensure data quality, a data

extraction checklist was carefully adapted from standardized ART intake and follow-up forms, nurses currently working in the ART clinic and who had ART training were recruited as data collectors, a one-day training was provided for both data collectors and supervisors, and the completeness of the recorded variables was double-checked by taking some measurements.

2.7 Data processing and analysis

Forms were collected and assigned a sequential number (code) to facilitate data entry after ensuring the data quality. Data was entered using Epi-data version 4.6 software, then transferred to Stata version 16 for statistical analysis. Consider inconsistencies, coding errors, completeness, accuracy, clarity, and missing values. were verified in the data Furthermore, the Emergency Nutritional Assessment (ENA) and WHO AnthroPlus software was used to assess the nutritional status of HIV-infected children (underweight [WAZ], stunting [HAZ], and wasting [WHZ]). Descriptive statistics, such as proportions, tables, figures, IQR, and graphs, were used to describe the study participants' characteristics. The Kaplan-Meier and log-rank tests were used to estimate survival times, and survival curves were compared between different exposure groups. The prevalence of opportunistic infection.

3 Results and Discussion

3.1 Socio-demographic characteristics of HIV-infected children on ART treatment

The final analysis included 389 HIV-infected children on ART. More than half of the study participants, 231 (59.4%), were females. 168 (43.2 percent) of the participants were between the ages of 5 and 9 enrolled in ART care. Most of study participants with caregiver marital status were married, accounting for 187 (48.1 percent) of the total sample. Regarding residence, 249 (64%) of children lived in cities. About 284 (73 percent) of parents' current status was live**.**

3.2 Clinical and treatment characteristics of HIV-infected children on ART treatment

298 (76.6 percent) of the study participants had a baseline CD4 count above the threshold. According to the WHO clinical stage at baseline, 346 (88.9%) of HIV-infected children were in stage I and II. Most of participants, 265 (68.1 percent), had baseline ambulatory functional status, and 345 (86.7 percent) had Hgb levels less than 10 g/dl. The majority of study participants (344 in total) did not experience treatment failure (88.4 percent). Approximately 189 (48.6 percent) had a history of PMTCT **(Table 2).**

3.3 Opportunistic Infections Incidence from HIV-infected children on ART treatment

The subjects in the study were followed for a set period, with a median of 67 months (IQR=58-76 months). The patient's minimum time was one month, and the maximum time was 77 months after ART treatment began. The total person-time observation was calculated to be 1283449 person-year. During the follow-up period, 56.22 percent (CI, 42.95 percent to 69.21 percent) of participants developed various infection opportunities.

Bacterial pneumonia was found to have the highest proportion of OIs development, 90(8.25 percent), followed by Chronic diarrhea 82(12.45 percent), Pneumocystis pneumonia 59 (12.59 percent), Pulmonary tuberculosis 57(10.46 percent), and others 1 (0.14 percent) (Figure 1).

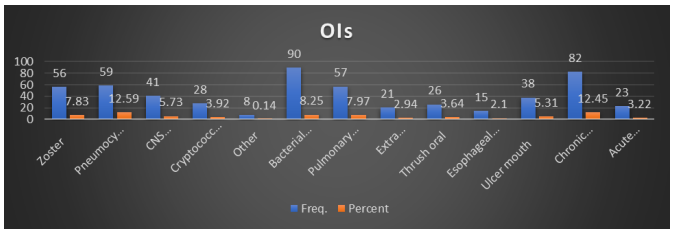

Fig 1. Frequency distribution of the type of OIs disease among HIV-infected children on ART treatment at University of Gondarcompressive Specialized Hospital, January 11, 2017, and January 10, 2022, (N = 389)

The overall Incidence of OIs was found to be 4.2 (95 percent CI 3.75 to 4.46) per 100 people year observation, with the Incidence of bacterial pneumonia being 13.5 (95 percent CI: 10.29,17.7), Zoster being 11.86 (95 percent CI: 0.96, 14.65), CNS

toxoplasmosis being 11.87 (95 percent CI: 0.87, 16.19), and Cryptococci meningitis being 10.88. (95 percent CI: 7.46,15.87) Pneumocystis pneumonia 13.94 (95 percent CI: 10.73, 18.12), thrush oral 10.58 (95 percent CI: 0.70, 15.92), chronic diarrhea 15.97 (95 percent CI: 0.96, 26.50), ulcer mouth 17.34 (95 percent CI: 12.62, 23.83), esophageal candidiasis 12.59 (95 percent CI: 10.17, 15.60), esophageal candidiasis 12.59

The cumulative probability of developing OIs among HIV-infected children who were free of any development at the start of the follow-up period was 0.9986, and there were no deaths (Figure 2).

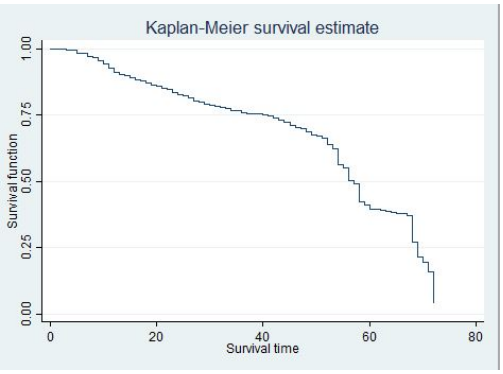

Fig 2. The Kaplan-Meier curve showing the cumulative probability of OIs disease among HIV-infected children on ART treatment at University of Gondar compressive Specialized Hospital, January 11, 2017, and January 10, 2022, (N = 389)

Predictors of opportunistic infections among HIV-infected children on ART treatment

Separate graphs were created to represent the Kaplan-Meier function estimates for some of the categorical variables (Figure 3). In each figure, the upper curve indicates that the particular group has a longer survival time than the one below. To determine whether there was a significant difference in opportunistic infections across different baseline CD4 count groups, this figure shows that the >200 cell/l baseline CD4 count group had a longer survival time than the 200 cell/l baseline CD4 count group one.

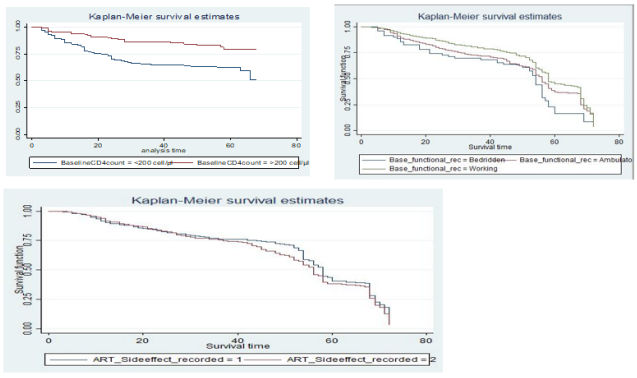

Fig 3. The Kaplan Meier Survival Curves for covariates curve showing CD4 count and functional status of HIV-infected children on ART treatment at University of Gondarcompressive Specialized Hospital, January 11, 2017, and January 10, 2022, (N= 389)

The log-rank statistical method was used to determine whether there is a significant difference in the survival functions shown using Kaplan Meier estimates of survival functions. The log-rank test revealed a significant difference in survival among educational status, occupation, prophylaxis, baseline CD4 count, functional status, ART side effect, and baseline WHO clinical

stage. However, there is no discernible difference between age and gender groups. HIV-infected children with >200 cell/l baselines CD4 count at the start of ART treatment had a longer survival experience than HIV-infected children with 200 cell/l baseline CD4 count, as supported by the log-rank test (log-rank Chi2(1) = 34.73, p-value=0.00).

HIV-infected children with WHO Clinical Stage I at the start.

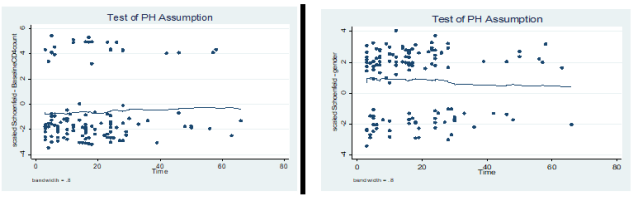

Fig 4. CD4 count and sex shenofelide test for type HIV-infected children on ART treatment at University of Gondar compressive Specialized Hospital, January11, 2017, and January 10, 2022, (N = 389)

3.5 Comparative analysis of models

Following confirmation of the proportional hazard assumption, semi-parametric and parametric proportional hazard models were fitted to estimate the Incidence of opportunistic infections and identify predictors in HIV-infected children. The most sparse model was chosen using information criterion (AIC, BIC) and log-likelihood results. The Gompertz regression model (AIC=1207.696, BIC=133.147, log likelihood= -576.8479) outperformed the Cox-PH and other parametric models in all three comparisons techniques. As a result, interpretations and conclusions were based on the Gompertz model.

After fitting a univariate Gompertz proportional hazard model, all predictor variables were found to have p-values of 0.2; after that, a multivariable model was fitted, and covariates such as baseline CD4 count, Hgb level, ART adherence, and ever taking IPT were found to be significant predictors of the Incidence of opportunistic infections among HIV-infected children at the 5% level of significance.

The risk of developing opportunistic infections is 2.05 times higher in HIV-infected children with a baseline CD4 count of 200 cells/l than in HIV-infected children with a baseline CD4 count of > 200 cells/l (AHR= 2.05). (1.40, 3.00).

The risk of developing opportunistic infections in HIV-infected children with 10 g/dl baseline Hgb level status is 5.87 times higher than in children with >10 g/dl baseline Hgb level status (AHR=5.87) (3.97,8.69).

The risk of developing opportunistic infections in HIV-infected children who have never received IPT is 1.71 times higher than in HIV-infected children who have never received IPT (AHR=1.71) (0.94, 3.11).

The risk of developing opportunistic infections is 1.41 times higher in HIV-infected children with fair/poor ART adherence than in HIV-infected children with good ART adherence (AHR=1.41) (0.90, 2.19).

This facility-based retrospective cohort study was conducted at the University of Gondar compressive and specialized hospital to determine the prevalence of common OIs among HIV-infected children on ART. Almost half of the study participants (56.22 percent) developed OIs, yielding an OI Incidence rate of 4.2 (95 percent CI 3.75 to 4.46) per 100 child-years of observation.

This finding is consistent with previous research from the United States of America (4.99 per 100 person-years)[17]. Similarly, our finding is significantly higher than that of previous studies from Latin America (1.1 per 100 person-years)[17] and Brazil (2.63 per 100 person-years)[18].

Similarly, our finding is significantly lower than studies from Ethiopia and Asia, which reported 9.7 (95 percent CI: 8.1, 11.5) per 100 child-years[13,19] and 10.5 per 100 person-years[20], respectively.

According to the literature, HIV-related OIs remain high in resource-limited settings, with SSA disproportionately affected[21]. Advanced technologies for early diagnosis, prevention, and management of OIs are available in developed countries. Additional explanations for the discrepancies mentioned above could be attributed to a lack of awareness among HIV-infected people living in developing countries about the importance of taking ART medications and OI prophylaxis continuously. Poverty, overcrowding, and malnutrition are common issues in developing countries, which may increase OIs among HIV-infected people. TB is the most common type of OI (29.8 percent) during the follow-up period. This finding is consistent with a study conducted in India, which found that TB is the most commonly diagnosed OI among HIV-infected individuals (34.6 percent). However, studies have revealed.

In our study, HIV/AIDS infected children with baseline Hgb levels less than 10 g/dl were increased by 5.87 times more than HIV/AIDS infected children with baseline Hgb levels greater than 10 g/dl (AHR=5.87) (3.97,8.69). This finding is also consistent with other research conducted at Debre Tabor Referral Hospital.

In our study, HIV/AIDS infected children with a history of ever taking IPT were 1.71 times more likely than HIV-infected children with no history of ever taking IPT (AHR=1.71) (0.94, 3.11). This study discovered that the risk of developing OIs was lower in HIV-infected children who received past OI prophylaxis compared to HIV-infected children who did not receive past OI prophylaxis. Previous Ethiopian research has revealed that prophylaxis is effective [(13)].

Finally, HIV-infected children with fair/poor ART adherence have a 1.41-fold higher AHR than HIV-infected children with good ART adherence (AHR=1.41) (0.90, 2.19). This study also discovered that ART drug adherence is a significant predictor of OIs. Children with "fair or poor" ART drug adherence were more likely to develop OIs than children with "good" ART drug adherence. A Cameron study discovered that HIV-infected children who did not adhere to ART therapy were more likely to develop OIs [(19)]. This study also found that OIs increased the risk of non-adherence significantly.

4 Conclusion

In this study, the rate of opportunistic infections among HIV-infected children was relatively low. OIs were discovered to be significantly related to variables such as baseline CD4 count, Hgb level, ART adherence, and use of IPT.

We believe that early screening and treatment of OIs should be considered as a result of the above findings. Furthermore, adherence assistance via phone calls and case managers could be enhanced. Furthermore, at each follow-up appointment, children with severe immunodeficiency and advanced disease stages at the time of ART initiation should be constantly observed and thoroughly evaluated for the Incidence of OIs.

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