ORIGINAL RESEARCH

Levels of Adherence and Associated Factors Among Children on ART Over Time in Northwest, Ethiopia: Evidence from a Multicenter Follow-Up Study

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Background: Despite the increased availability of antiretroviral therapy (ART), its success depends on a high level of adherence to a life-long antiretroviral therapy. However, the extent and factors associated with adherence to ART are not well known, especially in the current study setup. Therefore, this study aimed to assess the level of adherence and associated factors among children on ART in Northwest, Ethiopia.

Methods: A retrospective follow-up study was conducted on human immunodeficiency virus (HIV)-infected children receiving ART at South Gondar public hospitals. Children receiving ART from January 1, 2015, to November 30, 2020, were included in the study. A computer-generated simple random sampling technique was employed. The data were entered into the EpiData version 3.1 and analyzed by STATA 14 statistical software. Bivariable logistic regression was fitted for each predictor variable. Moreover, those variables having a p-value ≤0.25 in bivariate analysis were fitted into a multivariable logistic regression model. P-value <0.05 was used to declare significance.

Results: A total of 363 HIV-infected children were involved in the study. From 363 HIV-infected children, the level of adherence to ART was found to be 78.2%, 95% CI (73.6, 82.2). TB co-infection [adjusted odds ratio (AOR) = 3.8, 95% CI (1.41, 10.1)], short duration on ART (AOR = 3.4, 95% CI (1.60, 7.20)), treatment failure (AOR = 10.2, 95% CI (3.95, 26.2)), and Zidovudine containing ART regimen (AOR = 3.5, 95% CI (1.1, 10.9)) were significant predictors of poor adherence.

Conclusion: The current study showed that the level of adherence to ART was found to be low TB co-infection, short duration of ART, Zidovudine-containing ART regimen, and treatment failure were found to be significantly associated with poor adherence. Further studies on adherence rate and its determinants with multiple adherence measurements using prospective and multicenter studies were recommended.

Keywords: adherence, ART, children, Ethiopia

Background

Human Immunodeficiency Virus (HIV) is an RNA virus that causes Acquired Immune Deficiency Syndrome (AIDS),[1] which remains the leading cause of morbidity and mortality throughout the world.[2] Globally, 37.7 million people were living with HIV in 2020, 1.5 million new HIV infections, and 680.000 AIDS-related deaths.[3] Of this, HIV infection among children constitutes 4.5% of people living with HIV and 6.87% of total HIV/AIDS deaths.[3]

About 50% of children living with HIV/AIDS die before the age of 2 years as a result of recurrent opportunistic infections such as pneumonia, diarrhea,

malnutrition, and malaria.[4] According to the Summary of the global HIV epidemic (2019), Africa contributes 67.6% of the total HIV-infected people and 63.7% of the total HIV/AIDS deaths.[5]

As one of the African countries, the case in Ethiopia is not different. In 2016, there were 62.000 children aged <15 years living with HIV, 3800 newly diagnosed cases, and 2.900 deaths.[6] The introduction of effective antiretroviral (ART) treatment in the 1990s drastically reduced AIDS-related mortality and morbidity.[7] Ethiopia was among the first African countries to introduce ART in 2003 in selected health facilities following the issuance of the National Antiretroviral drugs (ARVS) supply and use policy in 2002.[8]

Antiretroviral therapy (ART) is a treatment for HIV that combines different types of antiretroviral medications, which should be taken throughout life to increase the length and quality of life for people living with HIV by reduction of the viral load and increase of the level of CD 4 cells.[9] The major factor determining the success of HAART is sustainable and optimum adherence to therapy[10] as poor adherence increases the risk of virologic failure, viral resistance, and dangerous outcomes such as substance abuse, depression, and spread of infections such as hepatitis.[11–14] Any patient who misses more than 3 dosages in a one-month treatment course is considered to have achieved suboptimal adherence which is less than 95%.[15]

Despite the increased availability of ART, implementation among children 0–14 years faces major challenges due to poor adherence.[16,17] Factors associated with pediatrics ART adherence can be related to caregivers, children themselves,[14,18–23] socioeconomic,[18,19] socio-demographic, and socio-cultural factors,[24,25] or service delivery issues,[18,19] It is also affected by high pill burden, poor palatability, long-term toxicity,[26,27] side effects of ARVs,[24–27] ART regimes,[14,18–21,25] drug dosing.[24,25] Duration on ART,[28] the health of the child,[29] child knowledge of their HIV status,[30] and psychosocial factors[17] have also been associated with pediatric ART adherence Unlike adults, young children rely upon their caregivers for their medicines.[18] Moreover, the experience of HIV-related rejections, non-acceptance, stigma, and discrimination minimize the patients' desire to maintain their optimal levels of health.[14]

The level of adherence to ART among HIV-infected children varied from 49% to 100% globally.[22] Similarly, in Ethiopia, it varied from 34.8%[31] to 95.5%[32] in Tikur Anbessa and Debre Birhan Referral Hospitals, respectively.

Ethiopia has adopted the 2014 UNAIDS 90-90-90 (90% of PLHIV know their status, 90% of PLHIV who know their status are on treatment (ART) and 90% of PLHIV on treatment have attained viral suppression by 2020) strategy.[33] However, only 79-71-87% have been achieved in 2018.[34] Although Ethiopia has been working a lot to attain the strategy since adherence is taken a lion's share to achieve the goal, poor level of adherence was greatly challenged especially in the study area.

Moreover, the risk factors of poor adherence were varied across the countries and the regions. Fortunately, most of the risk factors of poor adherence to ART are modifiable. Result determining the risk factors of poor adherence is a crucial role for intervention to reduce its magnitude and associated complication in the study area. As a result, this study aimed to determine the level of adherence to ART and its associated factors among children receiving ART at South Gondar public Hospitals, 2020.

Materials and Methods
Study Settings and Subjects
A retrospective follow-up study was conducted on HIV-infected children receiving ART at South Gondar public Hospitals. Children receiving ART from January 1, 2015, to November 30, 2020, were included. South Gondar public hospitals are found in Debre Tabor town which is the capital of South Gondar Zone in Amhara Regional State, Northwest Ethiopia. Debre Tabor Town is located 667 and 102 km far from Addis Ababa and Bahir Dar, respectively.[35]

South Gondar public hospital contained 05 hospitals that provide pediatric ART services. These hospitals are Debre Tabor compressive specialized hospital, Nefas Mewucha District Hospital, Mekane Eyesus District Hospital, Addis Zemen District Hospital, and Andabet District Hospital. As per the 2020 report, the total of HIV-infected children was 1312. The hospitals have a total of 71 Health care providers working at ART.

Source Populations
All HIV-positive children less than 15 years who had been taking ARV and were on follow-up from January 1, 2015, to November 30, 2020, at selected South Gondar public hospitals were the source population.

Study Population
Sampled children less than 15 years who had been taking ARV medications and were on following- from January 1, 2015, to November 30, 2020, at selected South Gondar public hospitals were the study population.

Inclusion Criteria
Children of less than 15 years who had been taking ART for a minimum of one month were included.

Exclusion Criteria
Participants who had incomplete data (that means charts without outcome variables and major explanatory variables) were excluded.

Sample Size Determination and Sampling Procedure
The sample size was calculated by using STATA 14 software of the two-population proportion formula taking the assumptions – 95% confidence level, 80% optimum statistical power, and taking type one error 5%. Taking male as exposure group from a previous study conducted in Mekelle Hospital, Ethiopia[36] denoted by q1 (0.82.0) and female non exposed group denoted by q0 (0.92.6), and then the total sample size, after adding 10% as incomplete or inconsistent data, will be 381. The hospitals were categorized into referral and district strata. Then, from the district hospitals stratum, Nefas Mewucha and Mekan Eyesus district Hospitals were selected randomly. From the referral hospital stratum, Debre Tabor specialized compressive specialized hospital was selected since it is the only specialized hospital in South Gondar Zone. Then, the sample size was allocated proportionally for each hospital. A simple random sampling technique was employed through a computer-generated system by taking the ART registration logbook as a sampling frame (Figure 1).

Operational Definitions
Poor adherence was defined as the percentage of drug dosage calculated from the total monthly doses of ART drugs <85%.[37]

A CD4 count: CD4 below the threshold level was classified based on the age of the child (i.e infants CD4<1500/mm^3, 12–35 months <750/mm^3, 36–59 months <350/mm^3 and ≥5 years <200/mm^3).[38]

Anemia was defined as having a hemoglobin level <10 mg/dl.[39]

Underweight or stunting was defined as weight for age Z-score < −2 SD for under-five children and BMI for age Z-score < −2 SD for older children.[40]

Data Collection Procedures
Data were collected using a pretested data abstraction format prepared from the national ART guidelines and by reviewing different kinds of literature. The abstraction tool was designed to collect information including socio-demographic, clinical, and treatment-related characteristics. The data were collected by three BSc nurses and supervised by two MSC pediatrics nurses. The training was given to data collectors and supervisors. The pre-test was done on 5% of the sample size in Addis Zemen district Hospital which is 57 kilometers away from Debre Tabor Town and one of the district hospitals in South Gondar.

Data Processing and Analysis
The data were entered into the EpiData version 3.1 and analyzed by STATA 14 statistical software.

Descriptive and summary statistics are explored through the table and figures. Finally, the outcome level adherence to ART was dichotomized into good or poor.

The bivariable logistic regression model was fitted for each predictor variable. Moreover, those variables having a p-value ≤0.25 in bivariate analysis were fitted into a multivariable logistic regression model. Adjusted odds ratios with 95% confidence interval and p-values were used to measure the strength of association and to identify statistically significant predictors. In multivariable analysis variables having P-value <, 0.05 were considered as significant predictors of poor adherence. The multicollinearity assumption was checked using the standard error and correlation matrix. Besides, Hosmer-Lemeshow statistics and Omnibus tests were performed, and Hosmer-Lemeshow's test was found to be insignificant (p-value = 0.483). While Omnibus tests were significant (p≤0.01) indicating the model was fitted.

Results
Socio-Demographic Characteristics of the Study Participants
A total of 381 medical records were reviewed among which 18 had incomplete data were excluded. Thus, a total of 363 children were included in the analysis which makes a completeness rate of 95.3%. The mean
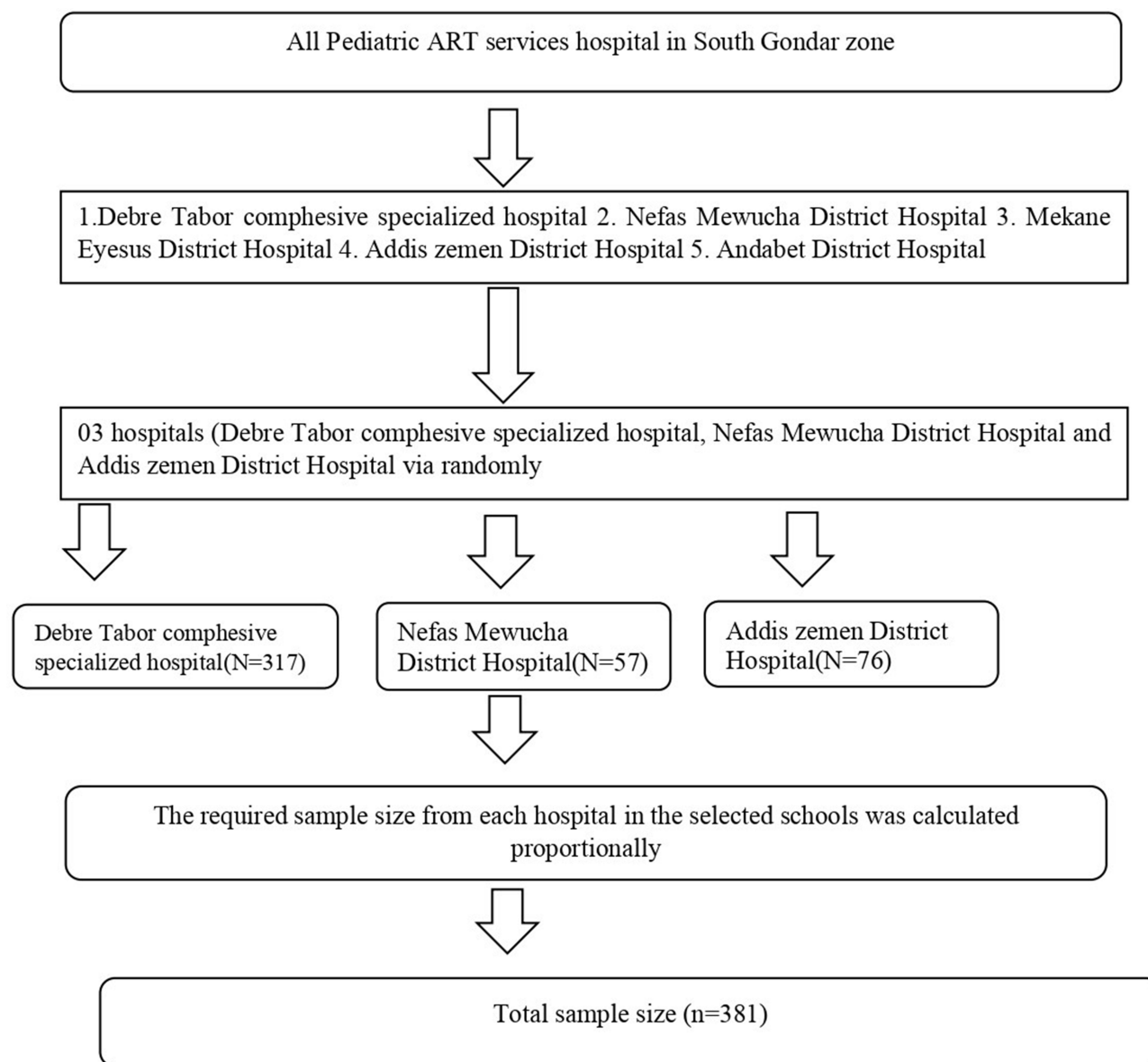
Figure 1 Schematic presentation of the recruitment and allocation process for adherence to antiretroviral among children receiving ART at South Gondar public Hospitals, Northwest, 2020.

age of the study participants was 7.34 (±3.4 SD) years, and 196 (54.0%) of them were in the age group of 5–9 years. Nearly half of 186 (51.2%) were males and 184 (50.7%) of children know their HIV status. Besides, 243 (66.9%) of caregivers were married and 52 (41.9%) cannot read and write whereas 99 (27.3%) had completed secondary school (Table 1).

Clinical and Treatment-Related Characteristics of Children on ART

Of 363 HIV-infected children, 186 (51.2%) were underweight, and 263 (72.5%) were WHO stage (I and II).

Seventy-one (19.6.3%) and 36 (9.9%) of study participants had a CD4 count below the threshold of and treatment failure, respectively. The majority (81.0%, n = 294) were on CPT users whereas 253 (69.7%) did not take IPT. Fifty-nine (16.3%) and 41 (11.3%) of the participants had anemia (<10 gm/dL) and TB, respectively. Two hundred forty (56.3%) of the study participants were on the Zidovudine-containing regimen and 231 (63.6%) were initiated ART before 2014. Regarding the duration of ART, 167 (46.0%) of study participants were taking ART > 59 months (Table 2). Finally, 79 (21.8%) of the study participants had poor adherence (Figure 2).

Table 1 Socio-Demographic Characteristics of Children Receiving ART at South Gondar Public Hospitals, Northwest, 2020 (n=363)

Variable	Categories	Number	Percent
Age of the child (years)	0–4	109	30.0
	5–9	196	54.0
	10–14	58	16.0
Sex	Male	186	51.2
	Female	177	48.8
Residence	Rural	73	20.1
	Urban	290	79.9
Marital status of caregivers	Single	49	13.5
	Married	243	66.9
	Widowed/ Divorced	71	19.6
Caregiver's educational status	Cannot read and write	152	41.9
	Primary school (1–8)	92	25.3
	Secondary school (9–12)	99	27.3
HIV disclosure Status	Yes	184	50.7
	No	179	49.3

Factors Associated with Poor Adherence to ART

In the bivariable logistic regression analysis residence, weight for height, hemoglobin level, WHO stages, CD4 counts, regimen type, cotrimoxazole preventive therapy (CPT), treatment failure, TB status, and duration on ART having P value less than 0.25 and fitted into a multivariable logistic regression model. In the multivariable model zidovudine regimen contained at baseline, presence treatment failure, presence of TB co-infection, and duration on ART <36 months were predictors of poor adherence.

The odds of children who were enrolled in zidovudine-containing ART regimen were (AOR=3.5, 95% CI: 1.1–10.9) three folds more likely to be poor adherent than their counterparts. The odds of being poor adherence among HIV-positive children on ART who had TB was around four higher than those who had no TB 3.8 (1.41–10.1) (OR= 3.8, 1.41–10.1). The odds of children on ART with treatment failure was around 10 times higher to be poor adherence than those who had no treatment failure (AOR= 10.2, 3.95–26.2); similarly, HIV-positive children on ART with <36 months on ART [OR = 3.4 (95% CI: 1.60, 7.20)]

Table 2 Clinical Characteristics of Study Participants Receiving ART at South Gondar Public Hospitals, Northwest, 2020 (n=363)

Variable	Categories	Number	Percent
Weight for height	Normal	177	48.8
	Underweight	186	51.2
Hgb level	<10mg/dl	59	16.3
	>10mg/dl	304	83.7
WHO stage	I & II	263	72.5
	III &IV	100	27.5
CD4 counts or %	Below threshold	71	19.6
	Above threshold	292	80.4
Regimen at baseline	Zidovudine contains	314	86.5
	Non-zidovudine contains	49	13.5
Cotrimoxazole preventive therapy (CPT)	Yes	69	19.0
	No	294	81.0
Isoniazid preventive therapy (IPT)	No	253	69.7
	Yes	110	30.3
Treatment failure	Yes	36	9.9
	No	327	90.1
TB status	Yes	41	11.3
	No	322	88.7
Year initiation	<2014	231	63.6
	≥2014	132	36.4
Duration on ART	<36 months	129	35.5
	36–59 months	67	18.5
	>59 moths	167	46.0
Follow-up status of Adherence	Good	284	78.2
	Poor	79	21.8

were more likely to poorly adhere to their ART >59 months in the follow-up period (Table 3).

Discussion

This study revealed that the level of adherence to ART in south Gonder public hospitals was found to be 78.9%. Besides, TB co-infection, short duration of ART, Zidovudine containing ART regimen, and treatment failure were found to be significantly associated with poor adherence.

The finding is comparable with the study conducted in Ethiopia (78.6%), Uganda (79%), Nigeria (76.1%), and Myanmar (76.2%).[41–44] However, this finding is higher than the studies conducted at Tikur Anbessa Hospital
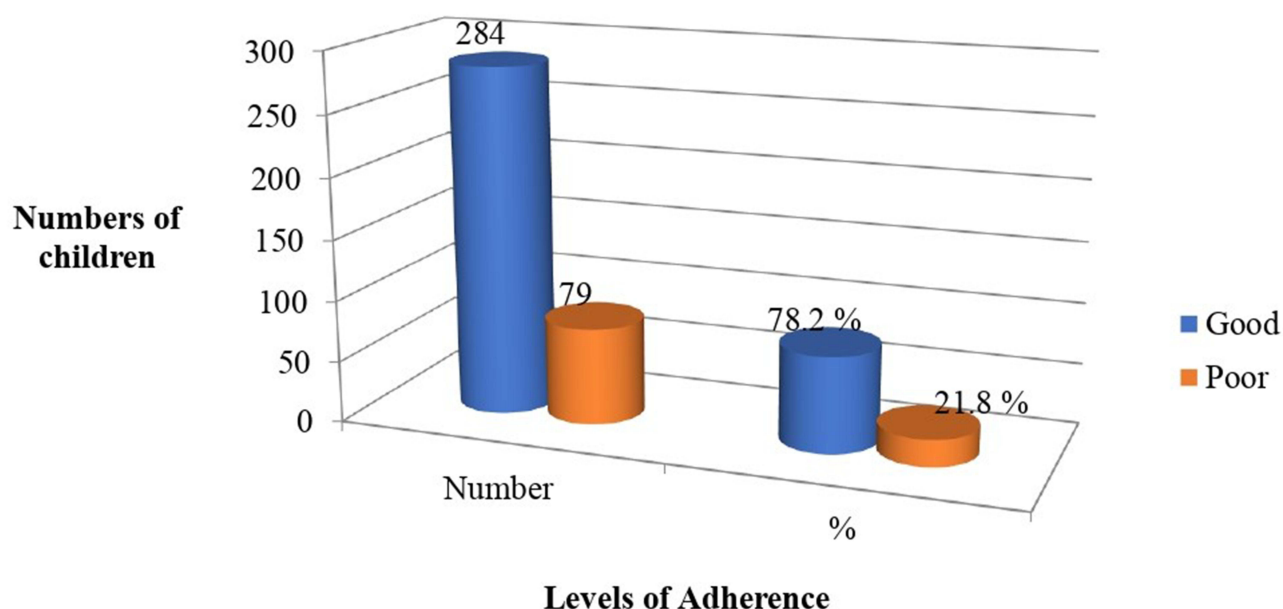
Figure 2 Levels of adherence of children receiving ART at South Gondar public Hospitals, Northwest, 2020.

(34.8%) and Jimma (63.8%).[31,45] Moreover, the level of adherence to ART is also higher than the studies conducted in Peru (41.7%), and Brazil (71.6%).[46,47] On the other hand, this finding is lower than the studies conducted in Debre Birhan (95.5%) and Nepal (87.4%).[32,48]

The discrepancy could be explained by the difference in diagnostic procedures of adherence to ART. In addition, under-reporting due to shortage of skills of healthcare providers or caregivers is usually encounter in low-income countries than in middle countries. Socioeconomic status, the study design, methods of adherence assessment, sample size, and setting difference are also considered for this variation.

This study showed that children having TB/HIV co-infection increase the level of poor adherence by 3.80 times than children without TB co-infection (AOR=3.80, 95% CI (1.41, 10.1)) which is in line with other studies.[43,47] This might be due to the summative effect of suffering from two chronic conditions, associated with stigma and discrimination that require clinical management for an entire life. In addition to this, medication for confection, treatment, and ART together can contribute to increased pill burden, drug–drug interactions, and more adverse drug effects, all of which are capable of hindering adherence to antiretroviral drugs.

This finding also showed that HIV-positive children on ART with <36 months on ART [AOR = 3.4 (95% CI: 1.60, 7.20)] were more likely to be poor adherents than children who were on ART > 59 months in the follow-up period Similar findings were reported from Tanzania[49] and Nepal.[48] The duration of treatment prolongs, quality of life improves which in turn motivates the children to have good adherence and to follow every instruction and recommendation provided by the health care providers and caregivers.

The odds of children on ART with treatment failure was around 10 times higher to be poor adherent than those who had no treatment failure (AOR= 10.2, 3.95–26.2). This is a similar report from a study conducted in South Africa.[50]

Treatment failure is the main cause of death, drug adaptability, and the development of drug-resistant viral strains which is potentiating challenge globally by reducing drug adherence. Furthermore, HIV drug resistance occurs when mutations develop frequently because of poor adherence (treatment interruptions, inadequate drug concentrations, or/and use of suboptimal drug combinations).[50,51] Besides, Poor adherence to ART is a major factor of treatment failure, the emergence of drug-resistant viruses, disease progression, hospitalization, mortality, and health care costs.[52]

834
HIV/AIDS - Research and Palliative Care 2021:13

Table 3 Bivariable and Multivariable Logistic Regression Analysis on Levels of Adherence Among Children Receiving ART at South Gondar Public Hospitals, Northwest, 2020 (n=363)

Variable	Categories	Level of Adherence		COR,95% CI	AOR, 95% CI
		Poor (79)	Good (284)		
Age of the child (years)	0–4 5–9 10–14	23 41 15	86 155 43	0.8 (0.36–1.62) 0.8 (0.38–1.50) 1	– – –
Sex	Male Female	42 37	144 140	1.1 (0.67–1.82) 1	– –
Residence	Rural Urban	28 51	45 239	2.9 (1.70–5.11)* 1	3.3 (0.96–7.25) 1
Marital status	Single Married Widowed/Divorced	8 54 17	41 189 54	0.6 (0.24–1.58) 0.9 (0.49–1.69) 1	– – –
Educational status	Cannot read and write Primary school (1–8) Secondary school (9–12)	40 22 16	112 70 83	1.9 (0.97–3.53) 1.6 (0.79–3.34) 1	0.7 (0.25–2.02) 0.6 (0.18–1.73) 1
HIV disclosure Status	Yes No	48 31	131 153	1.8 (1.1–3.00)* 1	0.7 (0.35–1.33) 1
Weight for height	Normal Underweight	25 54	152 132	1 2.5 (1.46–4.22)*	1 1.3 (0.66–2.61)
Hgb level	<10mg/dl >10mg/dl	21 58	38 246	2.3 (1.28–4.29)* 1	1.6 (0.68–3.71) 1
CD4 counts or %	Below threshold Above threshold	22 57	49 235	1.9 (1.04–3.31)* 1	1.4 (0.64–2.94) 1
WHO stages	I & II III &IV	39 40	224 60	1 3.8 (2.26–6.47)*	1 1.9 (0.85–4.10)
Regimen at baseline	Zidovudine contain Non-zidovudine contains	73 6	241 43	2.2 (0.89–5.30) 1	3.5 (1.1–10.9)** 1
CPT	Yes No	60 19	234 50	1 1.5 (0.81–2.70)	1 1.0 (0.42–2.12)
IPT	Yes No	21 58	89 195	1 1.3 (0.72–2.20)	- -
Treatment failure	Yes No	21 58	15 269	6.5 (3.16–13.4)* 1	10.2 (3.95–26.2)** 1
TB status	Yes No	24 55	17 55	6.9 (3.45–13.6)* 1	3.8 (1.41–10.1)** 1
Year initiation	<2014 ≥2014	50 29	181 103	0.9 (0.58–1.65) 1	- -
Duration on ART	<36 months 36–59 months >59 moths	48 10 21	81 57 146	4.1 (2.31–7.36)* 1.2 (0.54–2.75) 1	3.4 (1.60–7.20)** 1.6 (0.60–4.10) 1

Notes: *p value<0.05 at bivariable logistic regression: **p value<0.05 at multivariable logistic regression.

In the current study, the odds of children who were enrolled in the Zidovudine-containing ART regimen were (AOR=3.5, 95% CI: 1.1–10.9) three folds more likely to be poor adherents than their counterparts. This was also supported by the study conducted in Kenya.[53] The reason behind this might be that those who were on the Zidovudine regiment were more prone to severe life-threatening anemia, severe gastro-intestinal intolerance, fatigue, congestive heart failure, and sepsis/infection which leads to poor treatment adherence. However, inconsistent with studies from Oromia Ethiopia[54] that showed that receiving protease inhibitors were more likely to be poor adherent. Since ART drugs most likely need to be administered throughout the patient's life, a regimen should be chosen after considering the patient's characteristics, the results of viral drug resistance testing, drug efficacy, and ease of administration, potential AEs, pill size, and dosing frequency.

Limitation of the Study

While this study is multi-setting, the data on adherence were collected from a chart that was recorded according to the patient's self-report of the amount of medication taken between visits without a standardized set of questions. Being retrospective may also limit the study to evaluate the predictor's variable of adherence to ART includes caregiver's socioeconomic status.

Conclusion

The current study showed that the level of adherence to antiretroviral therapy was found to be low. TB co-infection, short duration of ART, Zidovudine-containing ART regimen, and treatment failure were found to be significantly associated with poor adherence. Based on our results, health care providers should provide intensive and ongoing counseling to a child and/or their caregivers before and throughout ART, training sessions are required to gain knowledge on disseminating information appropriate to a patient's level of understanding. It will empower patients with correct knowledge about good adherence practice. Despite the earlier presentation of children to care should be motivated, more targeted adherence support should be planned for those who present at an early stage of their illness. Besides this, children or their caretakers should be provided with adequate counseling during medication change or when new medication with a different role is added and establish a system of linkage with other units in the Hospital. For instance, in the case of TB co-infection, they should be linked with the TB unit and the children should take Anti-TB medication with ART

drugs. The hospital management team is also expected to provide training on ART adherence counseling to health care providers. Moreover, further studies should be conducted to evaluate and improve the quality of ART service in south Gondar public Hospitals.

Abbreviations

AIDS, Acquired Immune Deficiency Syndrome; AOR, Adjusted Odds ratio; ART, Anti-Retroviral Therapy; CPT, Cotrimoxazole Preventive Therapy; HIV, Human Immunodeficiency Virus; IPT, Isoniazid Preventive Therapy; TB, Tuberculosis; WHO, World Health Organization.

Ethical Approval and Participant Consent

Ethical clearance letter was obtained from an ethical review board of Debre Tabor University. In addition, a permission letter was also obtained from each south Gondar public hospital. Since we used secondary data, we did not get informed consent from the study participants. Confidentiality was secured. This study was conducted in accordance with the Declaration of Helsinki.

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. All authors read and approved the final manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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