

Children's Adherence to Antiretroviral Therapy and Associated Factors: Multi-center Cross-sectional Study

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Abstract

Background- Suboptimal adherence to antiretroviral therapy will lead to drug resistance, treatment failure, clinical deterioration, death and failure to thrive in children. Studies conducted among children below 15 years old were limited in Ethiopia in general and in the study area in particular. Therefore, this study aimed to assess the status of children's adherence to ART and associated factors in the study area.

Methods- We conducted a facility-based cross-sectional study by including 282 children <15 year who received anti-retroviral therapy for at least one month. All children/caregivers who were attending the ART clinic during the data collection period were consecutively recruited for the study. Both bivariate and multivariate logistic regression were performed.

Result- Out of 282 caregivers included with their children, 226 (80.2%) were females (mean age= 38.6 and SD = 12.35), and out of the total children, half (50%) were female and 246 (87.2%) were between the ages 5–14 years (mean age= 8.5 and SD = 2.64). Two hundred forty six (87.2%) children had an adherence status of ≥95% in the month prior to the interview. Children whose caregivers were residing in urban areas were 3.3 (95% CI: 1.17, 9.63) times more adherent to ART than those whose caregivers were residing in rural areas. Children whose caregivers were biological parents were 2.37(95% CI: 1.59, 3.3) times more adherent than those whose caregivers were non-biological parents. Additionally, children of caregivers who were knowledgeable about ART treatment, were 4.5(95% CI: 1.79, 9.8) times more adherent to ART than their counterparts.

Conclusion and recommendation- The adherence status of children in our study area was comparable. Being biological caregivers, residing in urban areas and knowledgeable about ART treatment facilitate adherence to ART. Ongoing education about treatment and further study with multiple adherence assessment methods were recommended.

Background

According to a global HIV/AIDS report, the status of adherence to ART among HIV infected children varied from 65% to 90% (1), 75% in developing countries(2) and 88.8% in Ethiopia(3).

An important factor in achieving treatment success is maintaining optimal adherence to ART (4–6). Adherence to antiretroviral treatment is defined as taking 95% or more of the prescribed doses on time and in the correct way, either with or without food (5,7).

Poor adherence to ART will lead to an increased risk of drug resistance, treatment failure and clinical deterioration with increased premature death in children(9,10,12).

The causes of poor adherence to ART among pediatric patients are complex and interrelated factors (i.e., total dependency of the child on caregiver for procurement and drug administration, pill burden and dosing frequency, treatment side effects, poor health literacy, poor patient-physician relationship limited

access to ART as a result of formulary restrictions(10–12), challenge related age, socioeconomic status of the caregiver, substance use and access to service delivery) (13) (14).

The emergency of drug resistant HIV virus among children adds an enormous burden since it may create an introduction of resistant HIV virus to the general population as the child with HIV grows to adolescence and young adulthood(15)(16).

As a result, designing strategies for maintaining the optimal status of adherence among children is essential to ensure treatment success. However, this task requires careful assessment of the status of adherence and age specific factors (17). However, studies conducted among children below 15 years of age are limited in Ethiopia in general and in the study area in particular. Additionally, adherence is not static and can vary with time on treatment, making assessing adherence status crucial(14). Moreover, viral load was added as one variable in this study which has not been researched in previous studies. Therefore, this study aimed to examine the status of adherence and associated factors among children under the age of 15 years in the study area.

Methods And Materials

A facility based cross sectional study was conducted from April 1 to May 10, 2020 in the Sebeta, Teji, Tullu Bollo and Waliso towns which are located 20 km,50 km, 65 km and 114 km away from Addis Ababa, respectively, in the southwestern direction along the main road from Addis Ababa to Jimma. In these four towns, there are 8 public ART sites, and all were included. Of those, three are within Sebeta town (Sebeta HC that serves 1135 HIV positive patients, of which 41 were children less than 15 years, Alembena HC that serves 395 patients, out of which 21 were children under the age of 15 and Tefki HC that give services for 112 patients in which 09 were children under the age of 15). Two public ART sites are found in Tullu Bolo town, Tullu Bolo General Hospital which serves 245 HIV positive patients, of which 25 were children, and Tullu Bolo HC which provides services for 17 HIV positive children. Teji town also has Teji HC who provide services for 230 HIV positive patients, of whom 18 were children under the age of 15. The rest are found in Waliso town, St. Lukes Referral Hospital which serves 1562 HIV infected patients, of whom 130 are children under the age of 15, and Waliso HC, which serves 801 HIV infected patients, of whom 29 are children below 15 years. In total, 290 children are on ART in those health facilities. All these health facilities have case managers and adherence supporters. After we calculated the sample size for both objectives (assessing adherence status and identifying factors), we selected the largest sample calculated by considering the ratio of unexposed to exposed 0.6, outcome in the exposed group 49%, and outcome in the unexposed group 29.5%(18), with a 10% nonresponse rate giving a sample size of 254. However, there were 290 children on ART in these health facilities, and all were included.

Pretested and structured questionnaires using face- to - face interviews were held for data collection. The questionnaires were adapted from previously conducted related studies and some changes were made after reviewing the relevant literature according to the local context and translated to Afan Oromo and

Amharic for better understanding by the respondents. Pretest of the questionnaire was performed on 5% (14) of the caregivers in Awash Health Center. Medical records were reviewed to collect clinical data such as WHO clinical stage, regimen type, viral load and the CD4 count of children. Data were collected by 8 clinical nurses. The data collection process was supervised by one health officer and one BSc nurse. Adherence and exposure variables were measured by the caregivers' or children's report of a one-month recall of missed doses prior to the date of the interview. The questionnaires were coded and entered into EPI data statistical software and then exported to SPSS Windows version 23 for further analysis. Data were summarized and presented using descriptive and analytic statistics. Bivariate and multiple logistic regressions were computed to identify the presence and strength of associations. Variables with a p value <0.25 in binary logistic regression were subjected to multiple logistic regression for further analysis. However, before taking variables for multiple logistic regression, multicollinearity was checked for all candidate variables using a collinearity diagnostic test and no multicollinearity (maximum Variance Inflation Factor (VIF) =3.883). Interaction was also checked by the Breslow-Day test, and a significant synergistic interaction was detected between two variables (i.e., blood relationship of the child with caregiver and caregiver taking ART). As a result, the stratum specific odds ratio was considered to measure the strength of the

association. At the end, multiple logistic regression (odds ratios with 95% CIs were computed) and variables with p-values less than 0.05 in the multiple logistic regression were considered significantly associated with the dependent variable. Finally, the model was fitted using the backward elimination method, and the Hosmer-Lemeshow goodness of fit test indicated that the model fit well (p- value 0.47).

Operational Definition

Adherent to ART – when the child has missed ≤ 1 dose or takes $\geq 95\%$ of ART in the month prior to the interview.

Non adherent to ART- missing at least two doses or takes <95% of ART in the month prior to interview.

Care givers- Parent/guardian or person in charge of routinely administering antiretroviral drugs to children on ART.

Baseline CD4 count- CD4 count done when a child started ART(7).

Current CD count- CD4 count done within 6 months of data collection(7).

Knowledge about ART- Those respondents who scored greater than or equal to the mean for the knowledge questions were considered knowledgeable; otherwise, they were not.

Care giver/child substance use- if caregiver/child use either of alcohol, khat, cigarettes or other substance in the month prior to data collection.

Ethical considerations

Ethical clearance letters were obtained from the Ethical Review Committee, Jimma University, Institute of Health. Each health facility was contacted after the official latter was submitted. The interviews were held after verbal informed consent and assurance of confidentiality.

Results

Sociodemographic characteristics of the study participants

Of the 290 study participants, 282 children along with their caregivers were included in the analysis, yielding a response rate of 97.2%. Four caregivers were excluded because they did not appear in the health facility during the data collection period. Three questionnaires were discarded as they were not complete (caregivers did not know the dosing history for the past month) and one caregiver was not willing to respond to the questionnaires. Among the respondents, 226 (80.2%) of the caregivers were females, and the mean age of the respondents was 38.6 years ($SD = 12.35$). Out of the total respondents, 176 (62.5%) were married and only 31 (11%) were single. One hundred fifty eight (56%) of the caregivers attended primary education. Two hundred nine (74.1%) of the caregivers were urban dwellers. Among the children included in the study, half (50%) were female, 246 (87.2%) were 5–14 years old and the mean age was 8.5 years ($SD = 2.64$). One hundred eighty three (64.9%) of the children are currently attending grade 1-4. (**Table 1**)

Table 1- Socio demographic characteristics of study participants, central Ethiopia, April 1- May 10, 2020. (n=282)

Variables		Frequency	Percentage
Sex of care giver	female	226	80.2
	male	56	19.8
Care giver age	<30yrs old	60	21.3
	>=30yrs old	222	78.7
Marital status of care giver	married	176	62.5
	widowed	53	18.8
	single	31	11.0
	Divorced	22	7.7
Educational status of care givers	Not educated	67	23.7
	Primary	158	56.0
	Secondary	48	17.4
	Tertiary	8	2.8
Religions of care givers	Orthodox	216	76.6
	Protestant	40	14.2
	Muslim	26	9.2
Care givers ethnicity	Oromo	231	81.9
	Amhara	38	13.4
	Gurage	13	4.7
Occupation of care giver	Self Employed	147	52.1
	Farmer	76	27.0
	Merchant	45	15.9
	Gov't employee	11	3.8
	Unemployed	3	1.1
Residence of care giver	Urban	209	74.1
	rural	73	25.9
Monthly income of care giver	<500 ETB	35	12.4
	>=500 ETB	247	87.6
Sex of child	Male	141	50.0
	Female	141	50.0
Age of child	0-4 yrs. old	36	12.8
	5-14 yrs. old	246	87.2
Educational status of child	Not eligible	33	11.7
	Not started	45	15.9
	KG	6	2.0
	1-4 grade	183	64.9
	5-8 grade	15	5.4

Clinical characteristics of study participants

Among the children who participated in this study, 102 (36.2%) started ART at WHO clinical stage I and 273 (96.8%) were currently on WHO stage I. At initiation of ART, 142 (50.4%) children had a CD4 count of >500 cells/mm³. From 206 (73%) children who had viral load counts, RNA of HIV virus was <1000 copies/ml in 151 (73.3%) children. (**Table 2**)

Table 2- Clinical characteristics of study participants, in central Ethiopia, April 1- May 10, 2020. (n=282)

Variables		No	%
Baseline CD4 count of the child	≤200	26	9.2
	201-499	54	19.2
	≥500	142	50.4
	Not done	60	21.2
Current CD4 count of the child	≤200	3	1.0
	201-499	13	4.6
	≥500	109	38.7
	Not done	157	55.7
WHO stage at Initiation of ART	WHO stage I	102	36.2
	WHO stage II	87	30.9
	WHO stage III	82	29.0
	WHO stage IV	11	3.9
Current WHO stage	WHO stage I	273	96.8
	WHO stage II	4	1.4
	WHO stage III	4	1.4
	WHO stage IV	1	0.4
Viral RNA Copies per ml	<1000	151	53.5
	≥1000	55	19.5
	Not done	76	26.9

ART and other drug history of the children

Among the children included in the study, 279 (95.8%) were on 1st line ART medication and 195 (69.2%) of the children were taking 2 pills per day (morning and night), while 38 (13.4%) of the children were taking 3 doses daily. The current study also showed that among children who took part in the study, 247 (87.6%) had been on ART for more than one year. Concerning CPT, 200 (70.9%) of the children were not on CPT at the time of data collection. (**Table 3**).

Table 3- ART and other drug history of study participants in central Ethiopia, April 1-May 10, 2020. (n=282).

Variables		No	%
Duration of child on ART	<1yrs	35	12.3
	=1yrs	247	87.6
Line of treatment	1 st line	270	95.8
	2 nd line	12	4.2
Number of pills child is taking/day	1 pills	38	13.4
	2 pills	195	69.2
	≥ 3pills	49	17.3
Is child taking CPT	Yes	82	29.0
	No	200	70.9

Out of the total children who are on ART in study the area, 176 (62.4%) of the children are prescribed AZT-3TC-NVP followed by the AZT-3TC-EFV based regimen, which accounts 47 (15.6 %). Only 6 (2%) of the children who are currently on ART have been taking a combination of AZT based kaletra (boosted drug with Protease inhibitor).

Adherence status of the children to ART

Based on the caregivers' report, a total of 246 (87.2%, (95% CI: 83.3%- 91.1%) children had an adherence status of ≥95% in the month prior to interview. The status of adherence to ART among children in the past three and seven days before the interview date was 98.9% and 95.8%, respectively.

Reasons for non-adherence

According to the current study, 36 (12.8%) of the children missed at least 2 doses out of their prescribed dose preceding for the month before data collection. The commonly mentioned reasons were: fear of stigma (21.3%), caregiver's forgetfulness (14.2%), and child's refusal to take the drugs (13.8%) and run out of medication (13.8%). (**Fig 1**)

Distance from health facility and mode of transportation

Out of the total caregivers/children who participated in the study, the majority, 219 (77.7%), came from less than 10 km and 113 (40.1%) of the participants came to the health facility on foot to refill medication. (**Table 4**)

Table 4- Distance from health facility and mode of transportation of study participant to refill medication, central Ethiopia, May 10, 2020.

Variables		No	%
Distance	< 10 km	219	77.7
	≥ 10 km	63	22.3
Mode of presentation	On foot	113	40.1
	By public bus	104	36.9
	By cart	22	7.8
	By Bajaj	43	15.3

Factors associated with adherence to ART

In multiple logistic regression, the residence area of caregivers, blood relationship between children and caregivers and knowledge of caregivers about ART treatment, were significantly and independently associated with adherence. Children whose caregivers resided in urban areas were 3.3 times more likely adherent to ART than their counterparts [AOR = 3.3(95% CI: 1.17, 9.63)]. Children whose caregivers were biological parents were 2.37 times more likely to be adherent than those whose caregivers were non-biological parents [AOR = 2.37(95% CI: 1.59, 3.2)]. The present study also showed that if the caregiver was knowledgeable about ART treatment, the child was 4.5 times more likely to be adhere to ART than their counterpart [AOR = 4.5(95% CI: 1.79, 9.8)]. (**Table 5**)

Table 4- Crude and adjusted odds ratios and 95% Confidence Intervals (CIs) of explanatory variables of adherence to HAART in the study area, central Ethiopia, April 1 May 10, 2020. (n=282).

Variables		Adherence status		Bivariate Logistic regression		Multiple logistic regression
		Adherent: N _o (%)	Non-adherent: N _o (%)	COR(95% CI)	P-value	AOR(95% CI)
Sex of care givers	male	46(82.1)	10(17.9)	0.6(0.27-1.32)	0.206	1.56 (0.51-4.73)
	female	200(88.5)	26(11.5)	1		1
Educational status of care givers	Not educated	48(71.6)	19(28.4)	1		1
	Primary	144(91.1)	14(8.9)	0.25(0.114-0.53)	0.000	0.3(0.45-1.97)
	≥ 9 Grade	54(94.7)	3(5.3)	0.14(0.04-0.504)	0.003	0.78(0.14-4.35)
Residence of care giver	Urban	187(89.5)	22(10.5)	2.02(0.97-4.19)	0.060	3.2(1.17-9.63)**
	rural	59(80.8)	14(19.2)	1		1
Monthly income of caregiver	<500 ETB	22(62.9)	13(37.1)	0.17(0.077-0.39)	0.000	0.45(0.15-1.34)
	≥=500 ETB	224(90.7)	23(9.3)	1		1
Educational status of child	Not eligible	26(78.8)	7(21.2)	1		1
	Not started	41(91.1)	4(8.9)	0.36(0.097-1.36)	0.133	0.35(0.005-24.0)
	KG-4 grade	165(87.3)	24(12.7)	0.54(0.211-1.38)	0.198	0.12(0.02-7.24)
	5-8 grade	14(93.3)	1(6.7)	0.27(0.03-2.38)	0.276	
Biological parent	Yes	213(95.1)	11(4.9)	14.67(6.6-32.59)	0.000	2.37(1.59-3.2)**
	No	33(56.9)	25(43.1)	1		1
Is care givers taking ART	Yes	203(94.9)	11(5.1)	10.73(4.9-23.45)	0.000	0.61(0.07-5.51)
	No	43(63.2)	25(36.8)	1		1
Knowledgeable	Yes	206(94.1)	13(5.9)	9.11(4.26-19.48)	0.000	4.9(1.7-9.8)**
	No	40(63.5)	23(36.5)	1		1
Viral RNA Copies per ml	<1000	136(90.1)	15(9.9)	1		1
	≥1000	42(76.4)	13(23.6)	2.8(1.24-6.37)	0.014	0.51(0.14-1.88)
	Not done	68(89.5)	8(10.5)	1.07(0.43-2.64)	0.889	

**---- significant variable

Discussion

According to this study, 87.2% of children had an adherence status of ≥95% in the month prior to the interview. This is higher than the finding of global pooled estimation (9). This difference could be due to the context of the study area (i.e., specific study area among children living in almost similar

Sociodemographic characteristics vs global context). In addition, the global pooled estimate used secondary data. However, our finding was comparable with a study conducted in East Africa, which showed 90%(19); in Southeastern Nigeria, 91%(20); Ethiopian national pooled prevalence of optimal HAART adherence 88.8% (3); Eastern Ethiopia which provided an adherence status of 90.7% (21), in Mekelle Hospital, Tigray, 90.7% (22); in Gondar University Hospital and Gondar Poly Clinic, 90.4%(23); and in Addis Ababa, 86.9%(24). However, the finding of the current study was higher than the finding of study conducted in India, which revealed an overall adherence of 82.1% (25). This difference might be due to the study design (cross-sectional vs cohort). It was also higher than that in a study in Uganda (overall adherence status of 79.1%)(26), South Wallo zone, which provided an adherence status of 78.6%(18), and in Fiche Hospital, which showed an adherence rate of 74%(27). This difference could be due to the small sample size (120) in Fiche Hospital compared to ours (282). Again, the current study finding was also greater than the finding of the study conducted in the ART clinic of Tikur Anbessa Hospital which showed that, the adherence rate of children to ART was 34.8%(28). This difference was due to adherence assessment methods (caregiver's report vs unannounced home based pill count). In general, the current study finding of the adherence status of children to ART is below the recommendation of the WHO, which recommended that $\geq 90\%$ of people on ART should be adherent to ART to fully benefit from ART(5).

Regarding associated risk factors for non-adherence, the current study showed that children whose caregivers were biological parents were 2.37 times more adherent than those whose caregivers were non-biological parents. [AOR= 2.37, 95 CI= (1.59-3.2)]. This finding is similar to the cross-sectional study finding conducted in Hiwot Fana and Dil-Chora Referral Hospital in eastern Ethiopia, which revealed that children whose caregivers were biological parents were more adherent.

The other independently associated risk factor for adherence to ART among children identified by this study was caregivers' knowledge of ART. Accordingly, we found that children with knowledgeable caregivers were 4.5 times more adherent than those children whose caregivers were not knowledgeable [AOR 4.5 95% CI (1.7-9.8)]. Our finding is similar to the study finding conducted in Hiwot Fana and Dil-Chora Hospital, which revealed that caregivers of children with good knowledge about the disease were 7.3 times [AOR = 7.3] adherent than their counterparts(21).

Again, our finding is also similar to the finding of a study conducted in India that came up with, children whose caregivers had good knowledge about ART treatment were 14.7 times more adherent (25). A similarly study conducted in south Wollo zone justified our finding [AOR=2.72] (34). Our finding is again in line with the study finding conducted at University of Gondar Hospital and Gondar Poly Clinic, which showed that children of knowledgeable caregivers had 4.7 times more adherent to ART than their counterparts [AOR=4.7](23). This implies that making caregivers knowledgeable about the importance of ART treatment through ongoing and extensive counseling is mandatory to make children more likely to benefit from good adherence to ART.

The current study also showed that children residing in urban areas were 3.2 times more adherent to ART than those residing in rural. [AOR=3.2, (95% CI 1.17-9.63)]. This finding is supported by a study conducted in Tanzania that reported, suboptimal to ART was observed among children in the rural context of the Mwanza region(29). However, our study is contradicts a comparative study conducted between rural and urban children, in South Africa that revealed, rural children were more adherent

to ART (93/1% vs 88%)(30). This difference might be due to the study design (cross-sectional vs cohort). In general, this implies that urban dwellers have more access to information and education than rural dwellers.

Our study is not free of limitations. There might be overestimation of adherence status in our study because of recall and social desirability bias. But we tried to minimize social desirability bias by using non ART providers as data collectors. Additionally, we did not assess adherence related to the correct timing of ART drug administration. Again, the cross-sectional nature of the study also hinders the causal relationship between adherence status and associated factors.

Conclusion And Recommendation

The adherence status of the children to ART in our study area was comparable. Children residing in urban areas, whose caregivers were biological parents and children of knowledgeable caregivers were more adherent to ART than those residing rural, children whose caregivers were not biological parents and whose caregivers were not knowledgeable. Ongoing counseling especially for non-biological parent and for those who come from rural areas at each follow up. Other researchers should also conduct another study by using multiple and more objective adherence assessment tools.

Declarations

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Competing of enterers

There is no competing of interest

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Figures

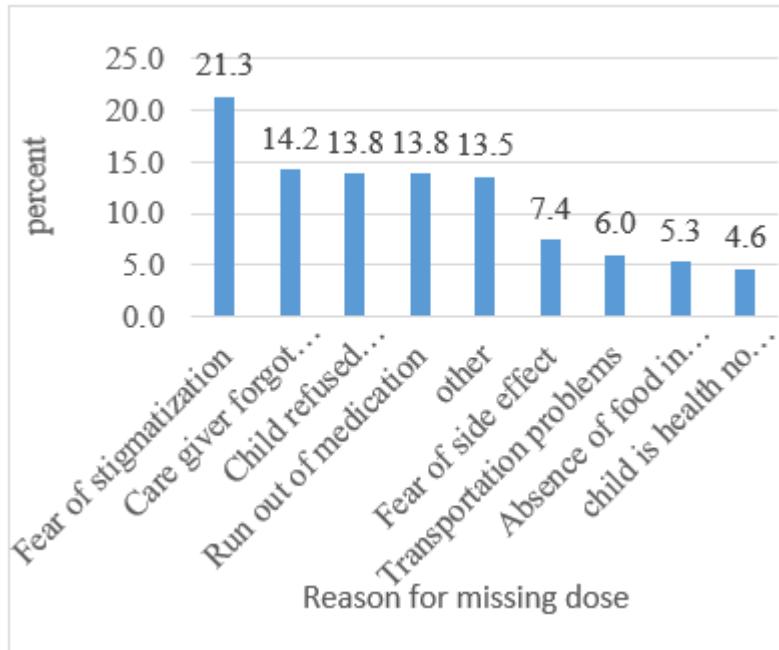


Figure 1

Reason for non- adherence to ART drugs among children in study area, central Ethiopia, April 1- May 10, 2020