

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

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## Research Article

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# Abstract

**Background-** Sub-optimal adherence to antiretroviral therapy will lead 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 study area in particular. Therefore, this study was aimed to assess status of children's adherence to ART and associated factors in study area.

**Methods-** We conduct a facility-based cross-sectional study by including total of 282 children <15 years, who received Anti retro viral therapy for at least one month. All children/caregivers who were attending ART clinic during data collection period were consecutively recruited to 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 adherence status of  $\geq 95\%$  in the month prior to interview. Children whose caregivers were residing in urban were 3.3 (95% CI: 1.17, 9.63) times more adherent to ART than those whose caregivers were residing in rural. Children whose caregivers were biological parent were 2.37(95% CI: 1.59, 3.3) times more adherent than those whose caregivers were non biological parent. Also 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 counter parts

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

## Background

According to 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 increased risk of dug resistance, treatment failure and clinical deterioration with increased risk of death in children(9,10,12).

The causes of poor adherence to ART among pediatric 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).

Emergency of drug resistance HIV virus among children adds an enormous burdens since it may create an introduction of resistant HIV virus to the general population as the child with HIV growing to adolescent and young adult(15)(16).

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

## Methods

Facility based cross sectional study was conducted from April 1 to May 10, 2020 in Sebeta, Teji, Tullu Bollo and Waliso towns that are found at 20km,50km, 65km and 114km away from Addis Ababa respectively, in south western direction along the main road from Addis Ababa to Jimma. In these four towns, there are 8 public ART sites and all were included. From those, three are within Sebeta town which include Sebeta HC that serves 1135 HIV positive patients, of which 41 were children less than 15 years, Alemgena 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 that serves 245 HIV positive patients of which 25 were children, Tullu Bolo HC that give services for 17 HIV positive children. Teji town has also, Teji HC that provide services for 230 HIV positive patients of which 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 which 130 are children under the age of 15 and Waliso HC which serves 801 HIV infected patients of which 29 are children below 15 years. Totally 290 children are on ART in those health facilities. All those health facilities have case managers and adherence supporters. After we calculated sample size for both objectives (assessing adherence status and identifying factors), we selected largest sample calculated by considering ratio of unexposed to exposed 0.6, outcome in exposed group 49%, outcome in unexposed group 29.5%(18), with 10% non -response rate giving sample size of 254. However, there were 290 children were on ART in these health facilities and all were included.

Pre-tested and structured questionnaires using face to face interview was held for data collection. The questionnaires was adapted from previously conducted related studies and some change was made after reviewing relevant literature according to local context and translated to Afan Oromo and Amharic for better understanding by the respondents. Pre-test of questionnaire was done on 5% (14) caregivers in Awash Health Center. Medical records was reviewed to collect clinical data such as WHO clinical stage, regimen type child is on, viral load and the CD4 count of children. Data was collected by 8 clinical nurse. 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 was 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 p value <0.25 in binary logistic regression were taken to multiple logistic regression for further analysis. But, before taking variables to multiple logistic regression, multicollinearity was checked for all candidate variables using collinearity diagnostic test and no multicollinearity (maximum Variance Inflation Factor (VIF) =3.883). Interaction was also checked by Breslow-Day test and significant synergetic interaction was detected between two variables (i.e. blood relationship of the child with caregiver and caregiver taking ART). As a result, stratum specific odds ratio was considered to measure strength of association. At the end multiple logistic regression, odds ratio with 95% CI was computed and variables having p-values less than 0.05 in the multiple logistic regression models were considered significantly associated with the dependent variable (adherence). Finally model was fitted using backward elimination method and Hosmer-Lemeshow goodness of fit test indicated that model is fitted well (p- value of 0.47).

## **Operational Definition**

**Adherent to ART** – when the child has missed  $\leq 1$  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 as knowledgeable, otherwise not.

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

## **Ethical considerations**

Ethical clearance letter is obtained from the Ethical review committee, Jimma University, institute of health. Each health facilities was contacted after official letter summited. Interview had been held after informed verbal consent and assurance of confidentiality.

## **Results**

## Socio-demographic 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 as they did not appear in the health facility during 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 respondents, 226(80.2%) of the caregivers were females and the mean age of the respondents was 38.6 and SD =12.35. Out of the total respondent, 176 (62.5%) were married and only 31(11%) were single. One hundred fifty eight (56%) of the caregivers have 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 and 246(87.2%) were in the age of 5–14 years with the mean age of 8.5 and 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 participated in this study, 102(36.2%) started ART at WHO clinical stage I and 273(96.8%) were on WHO stage I currently. At initiation of ART, 142(50.4%) children had a CD4 count of >500 cells/mm<sup>3</sup>. From 206 (73%) children who had viral load count, RNA of HIV virus were <1000 copies /ml in 151(73.3%) children. (Table 2)

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

Variables		No	%
Base line 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 children included in the study, 279(95.8%) of the children are on 1<sup>st</sup> line ART medication and 195(69.2%) of the children are taking 2 pills per day (morning and night) while, 38(13.4%) of the children are taking 3 doses daily. The current study also showed that, among children who took part in the study, 247(87.6%) have 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 at 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 <sup>st</sup> line	270	95.8
	2 <sup>nd</sup> 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

### Distance from health facility and mode of transportation

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

*Table 4-distance from health facility and mode of presentation to refill medication central Ethiopia, May 10, 2020.*

Variables		No	%
Distance	< 10km	219	77.7
	≥ 10km	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

Out of the total children who are on ART in study area, 176(62.4%) of the children are prescribed with AZT-3TC-NVP followed by, AZT-3TC-EFV based regimen which account 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 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 children missed at least 2 doses out of their prescribed dose preceding for the month before data collection. The commonly mentioned reasons for missing ART medications 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)

### **Factors associated with adherence to ART**

In multiple logistic regression, 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 were residing in urban area were 3.3 times more likely to be adherent to ART than their counterparts [AOR = 3.3(95% CI: 1.17, 9.63)]. Children whose caregivers were biological parent were 2.37 times more likely to be adherent than those whose caregivers were non biological parent [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 adherent to ART than their counter part [AOR = 4.5(95% CI: 1.79, 9.8)]. **(Table 5)**

*Table 5- Crude and adjusted odds ratio and 95% confidence interval (CI) of explanatory variables of adherence to HAART at study area, central Ethiopia, April 1 May 10, 2020. (n=282).*

Variables		Adherence status		Bivariate Logistic regression		Multiple logistic regression
		Adherent: N <sub>0</sub> (%)	Non-adherent: N <sub>0</sub> (%)	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 have an adherence status of  $\geq 95\%$  in the month prior to interview. This is higher than the finding of the study conducted by Lisa M. et al which showed that a global pooled estimates adherence of children to ART was 65% (9). This difference could be due to the context of study area in which we conducted study (i.e. specific study area among children living almost similar socio demographic characteristics and life style), but the global pooled estimates was conducted as global context. Besides, global pooled estimates used secondary data. But our finding was comparable with study conducted in East Africa showed 90%(19), Southeastern Nigeria 91%(20), Ethiopian national pooled prevalence of optimal HAART adherence was 88.8% (3), Eastern Ethiopia that provided adherence status of 90.7% (21), in Mekelle hospital, Tigray 90.7% (22), in Gondar University Hospital and Gondar Poly Clinic, 90.4%(23), Addis Ababa 86.9%(24). But the finding of current study was higher than the finding of the study conducted by Govind M. et al in India, that revealed an overall adherence of 82.1% (25). This difference might be due to study design (cross sectional vs cohort). It was also higher than study in Uganda (overall adherence status of 79.1%)(26), South Wallo zone which provided an adherence status of 78.6%(18), in Fiche Hospital that showed adherence rate of 74%(27). This difference could be due to the fact small sample size (120) in Fiche Hospital as compared to ours (282). Again the current study finding was also greater than the finding of study conducted in ART clinic of Tikur Anbessa Hospital that showed adherence rate of children to ART was 34.8%(28). This difference due to adherence assessment methods (caregiver's report vs unannounced home based pill count). In general the current study finding of adherence status of children to ART is below the recommendation of WHO which recommended that  $\geq 90\%$  of people on ART should be adherent to ART in order to fully benefit from ART(5).

Regarding associated risk factors for non-adherence, current study provided that children whose caregivers were biological parent were 2.37 times more adherent than those whose caregivers were non biological parent. [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 eastern Ethiopia that revealed children whose caregivers were biological parent were more adherent.

The other independently associated risk factor for adherence to ART among children identified by this study was care givers 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 that revealed caregivers of children with good knowledge about the disease were 7.3 times [AOR = 7.3] adherent than their counter parts(21). Again our finding is also similar to the finding of study conducted in India that came up with, children whose caregivers have good knowledge about ART treatment were 14.7 times more adherent (25). Similarly study conducted in south Wollo zone was justify 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, Northwest Ethiopia, 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 to be knowledgeable about the importance of ART treatment through ongoing and extensive counselling is mandatory to make a children more beneficiary from a good adherence to ART.

Current study also provided that children residing in urban area were 3.2 times more adherent to ART than those who residing in rural. [AOR=3.2, (95% CI 1.17-9.63)]. This finding is supported by the study conducted in Tanzania that reported us suboptimal to ART was observed among children in rural context of Mwanza region(29). But our study is contradicting with comparative study conducted between rural and urban children, south Africa toward ART adherence revealed that rural children were more adherent to ART (93/1% vs 88%)(30). This difference might be due to study design (cross sectional vs cohort). In general, this implies that urban dwellers have more access to information and education when compared to rural dwellers and this may expose them to be adherent than rural resident as they get knowledgeable about the importance of ART adherence due to accessibility of information.

Our study is not free of limitation. 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. Also we did not to assess adherence related to correct timing of ART drug administration. Again the cross sectional nature of the study also hinders causal relationship between adherence status and associated factors.

## **Conclusion And Recommendations**

Adherence status of the children to ART in our study area was comparable. Children residing in urban area, whose caregivers were biological parent and children of knowledgeable caregivers were more adherent to ART compared to those residing in rural area, children whose caregivers were not biological parent and children whose caregivers not knowledgeable.

Adherence supporter and health care provider in each health facility should enhance extensive and ongoing education toward the importance of good adherence to ART especially for non-biological parent and for those who come from rural area at each follow up. ART provider should attempt to regularly remind caregivers about the importance of ART and adherence to medication. Another researchers should also conduct another study by using multiple and more objective adherence assessment tool.

## **Declarations**

### **Competing interests**

The authors declare that they have no competing interests.

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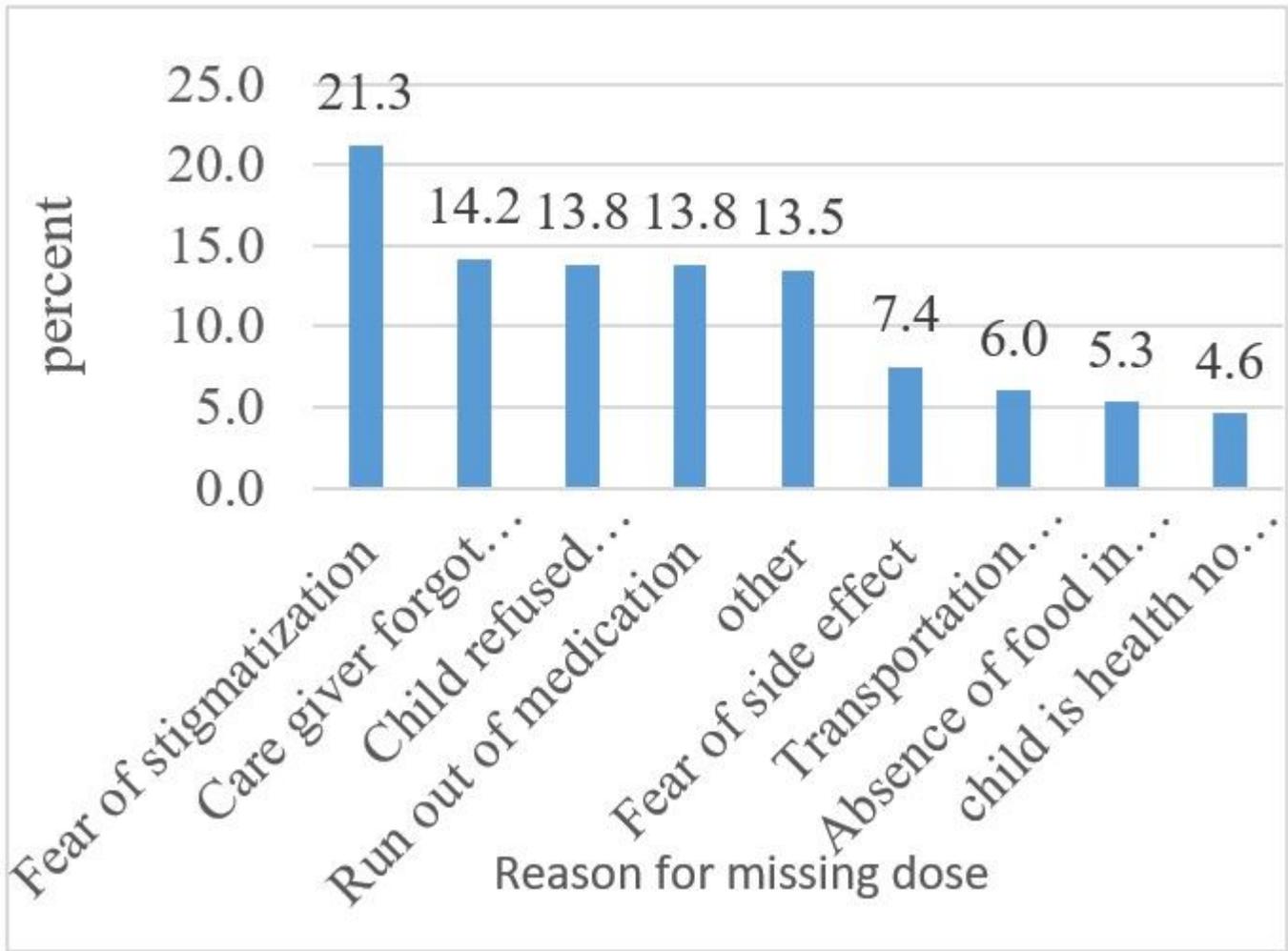
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## Figures



**Figure 1**

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