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Caregiver-Reported Antiretroviral Therapy non-adherence during the first week and after a month of treatment initiation among children diagnosed with HIV in Ethiopia

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To achieve optimal virologic suppression for children undergoing antiretroviral therapy (ART), adherence must be excellent. This is defined as taking more than 95% of their prescribed doses. To our knowledge, no study in Ethiopia has evaluated the level of treatment adherence at the beginning of the child's treatment. Our aim was therefore to evaluate caregiver-reported ART non-adherence among children and any predictors for this during the early course of treatment. We conducted a prospective cohort study of 306 children with HIV in eight health facilities in Ethiopia who were registered at ART clinics between December 20, 2014 and April 20, 2015. The adherence rate reported by caregivers during the first week and after a month of treatment initiation was 92.8% and 93.8% respectively. Our findings highlight important predictors of non-adherence. Children whose caregivers were not undergoing HIV treatment and care themselves were less likely to be non-adherent during the first week of treatment (aOR= 0.17, 95% CI: 0.04, 0.71) and the children whose caregivers did not use a medication reminder after one month of treatment initiation (aOR= 5.21, 95% CI: 2.23, 12.16) were more likely to miss the prescribed dose. Moreover, after one month of the treatment initiation, those receiving protease inhibitor (PI) (LPV/r) or ABC based treatment regimens were more likely to be non-adherent (aOR= 12.32, 95% CI: (3.25, 46.67)). To promote treatment adherence during ART initiation in children, particular emphasis needs to be placed on a baseline treatment regimen and ways to issue reminders about the child's medication to both the health care system and caregivers. Further large scale studies using a combination of adherence measuring methods upon treatment initiation are needed to better define the magnitude and predictors of ART non-adherence in resource limited settings.

Keywords: ART non-adherence, caregivers, children, predictors, HIV, Ethiopia

Introduction

The introduction of antiretroviral therapy (ART) contributed to improved survival of children living with HIV (UNAIDS, 2016). Its continued positive clinical impact depends on taking more than 95% of prescribed doses (Jobanputra et al., 2015; WHO, 2013; Zoufaly et al., 2013; Bhattacharya & Dubey, 2011; MOH, 2007). Several factors affect the rate of treatment adherence among children including drug regimen, caregivers, and society and culture related factors (Castro, Gonzalez, & Perez, 2015; Haberer & Mellins, 2009) (Hagstromer, Lundstedt, Balcha, & Bjorkman, 2013; Muller et al., 2011), (Reda & Biadgilign, 2012). Of these factors, the level of commitment of caregivers highly determines the degree of treatment success among children (Castro et al., 2015; Haberer & Mellins, 2009; WHO, 2013), as medication administration depends on a family caregiver (Muller et al., 2011).

Previous studies on this topic focused on adults only and they employed either cross-sectional or retrospective designs. Studies from Ethiopia reported that ART treatment adherence in children ranged from 78.6% to 93.3% (Arage, Tessema, & Kassa, 2014; Biadgilign, Deribew, Amberbir, & Deribe, 2008; Biressaw, Abegaz, Abebe, Taye, & Belay, 2013). A study conducted in sub-Saharan Africa indicated that ART adherence during the first six months of treatment predicted the prognostic value of virological and immunological responses and subsequent survival among adults (De Luca et al., 2012). No study in Ethiopia has evaluated the level of treatment adherence in the beginning of a child's treatment. Our aim was therefore to evaluate caregiver-reported ART non-adherence and its predictors among children in the early stages of treatment.

Methods

Study design

This was a cross-sectional study conducted at eight health facilities in Oromia and Addis Ababa regions of Ethiopia, forming a baseline for an ongoing cohort study. The minimum sample size was expected to be 300 including a 20% non-response rate.

Participants

Participants included family caregivers or responsible guardians aged 18 or above with a child aged between 3 months and 14 years newly registered for ART between December 20, 2014 and April 20, 2015. They were enrolled in the study within the first month of the child's ART treatment. Participants were coming to the facility every week in the first month and every month thereafter. The family caregivers were a parent, sibling, extended family member or legal guardian who had the main responsibility for regularly taking care of the child undergoing treatment. A child could have more than one caregiver in the family but only the primary caregiver was invited to participate.

At each clinic, data were collected by an ART provider assisted by a data clerk during the first week and at the end of the month of child's regular visit. They all received one-day training in the standard operating procedures for data collection. Based on instruments used in similar studies, a study-specific questionnaire was adopted in addition to a protocol for documenting data. We used Self-Reported Adherence questionnaire as it was suggested to be a useful instrument for assessing ART adherence (Munoz-Moreno et al., 2007). The questionnaire addressed socio-demographic, socioeconomic and disclosure variables of caregivers and children as well as the child's adherence to treatment. The protocol included clinical markers of the child including baseline CD4 count and WHO staging; and variables concerning the child's treatment regimen during treatment initiation and the caregivers' care

and treatment status. The instruments were piloted with two caregivers and their children and smaller modifications were made. Data were collected after seven and then thirty days of initial treatment.

In this study ART adherence rate was calculated as:

Doses prescribed – doses missed x 100

Doses prescribed

Children were said to be non-adherent with ART if they took <95% of the prescribed doses for one week and thirty days prior to the interview.

Data analysis

The IBM Statistical Package for Social Sciences (SPSS) version 22.0 was used for data entry and analysis (IBM Corporation, Armonk; NY, USA). Descriptive statistics were used to describe frequencies and proportion of caregiver and child characteristics. Levels of adherence dichotomized as non-adherent versus adherent at first week and first month and were the main outcome variables. Variables with $p < 0.25$ in the univariate analysis were included in the multivariate analysis. We performed multivariate analysis using the binary logistic regression method and described measures of association as odds ratios (ORs) with 95% CI. Statistical significance was set at $p < 0.05$.

Ethical consideration

The Swedish Regional Ethics Board (Ref. no. 2013/85) and the National Research Ethical Review Committee (Ref. no. 3.10/322/05) in Ethiopia gave formal approval. Written consent was obtained from all caregivers. Confidentiality was assured and explanation of the purpose and possible benefits and disadvantages of the study were provided.

Results

Socio-demographic characteristics

Of 306 caregivers and their children approached, three caregivers refused to participate making the response rate 99%. Most (82%) were females and 73% of the caregivers were biological parents or legal guardians of the children. Of the caregivers, 55% had disclosed their own HIV status to their family or others.

Over a half (52%) of the children were boys. The median age of children at ART initiation was 9 (IQR=6-12) years. Of those aged 6 years and above, 37% had been disclosed with their HIV diagnosis. Table 1 summarizes baseline characteristics.

Table 1. Baseline characteristics of study participants and study health facilities, Ethiopia.

Participant category and characteristics	n	%
Caregivers		
Sex		
Female	250	82
Male	56	18
Age (years)		
18-24	27	9
25-34	122	40
35-44	108	35
>44	49	16
Religion		
Muslim	27	9
Christian Orthodox	245	80
Christian Protestant	33	11
N/A	1	0.3
Marital status		
Married	161	53
Widowed/Divorced	99	32
Single	46	15
Educational status		
Literate	31	10
College/University level	31	10
Grades 1-8 completed	109	36
High School completed	84	28

Illiterate	51	17
Residence		
Urban	281	92
Rural	25	8
Employment		
Employee	130	43
House wife	81	27
Daily labourer	54	17.6
Unemployed	24	8
Other	17	6
Children	no	%
Sex		
Female	148	48
Male	158	52
Age when ART initiated (year)		
0-3	42	14
4-8	86	28
9-14	178	58
Schooling (age \geq 3 years, n=275)		
No	40	15
Yes	235	86
HIV disclosure (age \geq 6 years, n=231)		
Disclosed	85	37
Not disclosed	146	63
Study Health facilities		
Addis Ababa		
Black lion Hospital	32	10.5
ALERT Hospital	63	20.6
Zewuditu Hospital	66	21.6
Yekatit 12 Hospital	36	11.8
Oromia		
Bishoftu Hospital	26	8.5
Adama Hospital	28	9.2
Adama Health Center	29	9.5
Mojo Health Center	26	8.5
Total	306	100.0

Children whose caregivers were not undergoing HIV care and treatment themselves were less likely to be non-adherent (aOR= 0.17, 95% CI: 0.04, 0.71). After a month of treatment initiation, those receiving protease inhibitor (PI) (LPV/r) or abacavir (ABC) based treatment

regimen (aOR= 12.32, 95% CI: 3.25, 46.67) and the children whose caregivers did not use a medication reminder (aOR= 5.21, 95% CI: 2.23, 12.16) were more likely to be non-adherent (Table 2).

Table 2: Predictors of ART Non-adherence during the first week and after a month of treatment initiation among the caregivers' children.

Predictors of non-adherence	Adherence status, n (%)		cOR 95 % CI	aOR* 95 % CI
	In the first week of treatment initiation	Adherent		
Child age at ART initiation				
0-3	36 (85,7)	6 (14,3)	3,13(1,05, 9,34)*	1,97(0,55, 6,96)
4-8	79 (92)	7 (8)	1,66(0,59, 4,63)	1.14(0,38, 3,43)
9-14	169 (95)	9 (5)	1	1
Caregivers on ART themselves during the first week				
No	105 (97,2)	3 (2,8)	0,27 (0,08, 0,93)*	0.17(0,04, 0,71)*
Yes	179 (90,4)	19 (9,6)	1	1
After one month of treatment initiation				
Child age at ART initiation				
0-3	38(90.5)	4(9.5)	1.46(0.45, 4.76)	1.32(0.29, 6.05)
4-8	83(96.5)	3(3.5)	0.50(0.14, 1.83)	0.52(0.12, 2.24)
9-14	166(93.3)	12(6.7)	1	1
Child's base line treatment regimen				
4a/4b or 4c/1c/4d	225 (96)	9 (4)	1	1
1e (TDF+3TC+EFV)	34 (89.5)	4 (10.5)	2.94 (0.86, 10.08)	2.43(0.63, 9.39)
Other (LPV/r or ABC) based regimen	28 (82)	6 (18)	5.36 (1.77, 16.18)*	12.32(3.25, 46.67)*
Predictors of ART adherence among the caregivers' children in terms of missing prescribed doses				
	Missed no doses in the first month	Missed at least 1 dose in the first month		
After one month of treatment initiation				
Caregiver relation				
Biological Parents	178(79.5)	46(20.5)	1, 66(0.82, 3.40)	1.64(0.70, 3,81)
Non-Biological Caregivers	71(86.6)	11(13.4)	1	1
Child age when ART initiated				
0-3	33(78.6)	9(21.4)	1,46(0.63, 3.39)	1.20(0.50, 2.88)
4-8	66(76.7)	20(23.3)	1,62(0.85, 3,09)	1.37(0.69, 2,71)
9-14	150(84.3)	28(15.7)	1	1
Medication reminder				
No	16(55.2)	13(44,8)	4,30(1.93, 9,57)*	5.21(2.23, 12,16)*
Yes	233(84.1)	44(15,9)	1	1

Care-giver reported level of ART adherence

According to the caregivers' report, 93% and 94% of the children adhered to their prescribed ARV regimen in the first seven days and during the first month of treatment respectively. In terms of missing doses, 19% of children missed at least one or more doses during the first month after treatment initiation.

The major reason reported by caregivers for missing an ARV dose during the first month of the child's treatment was forgetfulness, as reported by 46%, see Figure 1

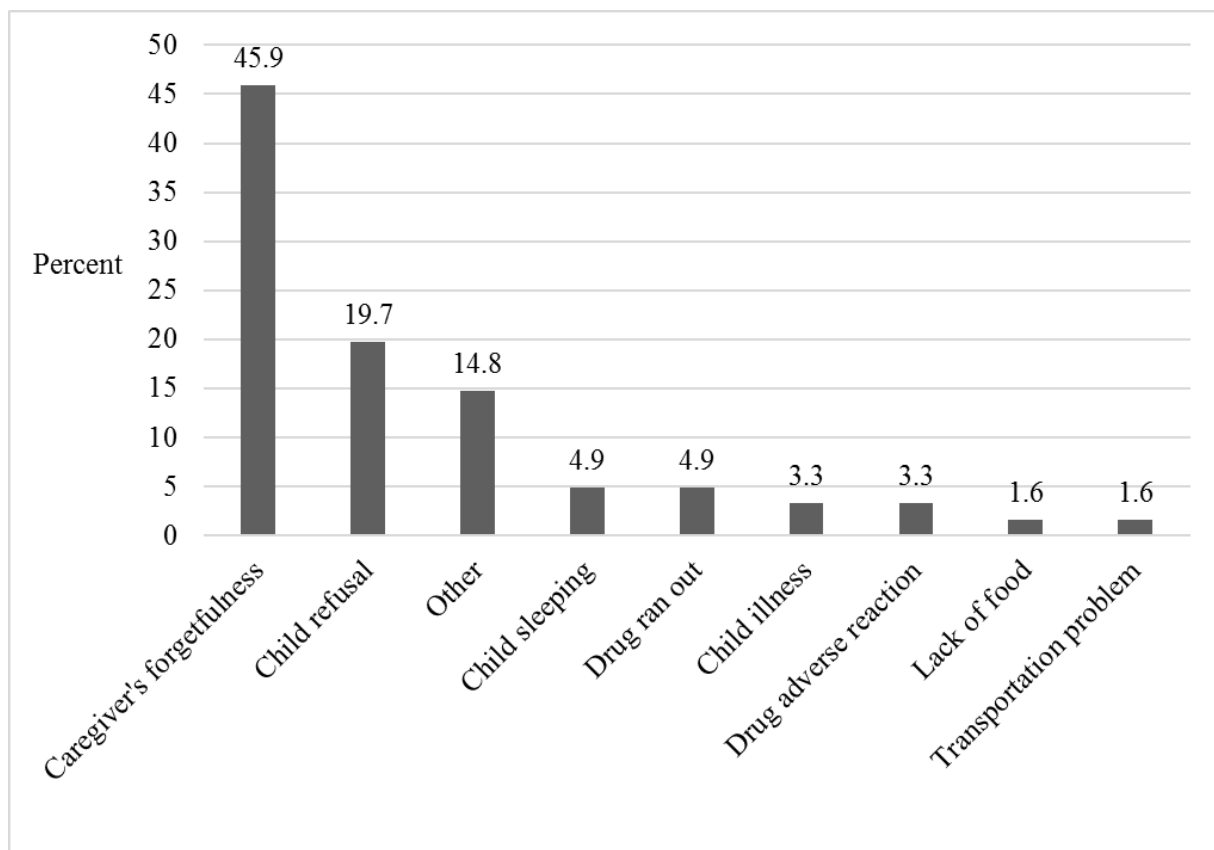


Figure 1. Reasons for missing doses stated by caregivers of children on ART

Discussion

In this study, > 90% of children received $\geq 95\%$ of prescribed doses after the first week and month of treatment initiation but missed doses were reported in about 19% of children. The most common reason for missing doses was care-givers' forgetfulness. The use of treatment reminders was associated with better adherence while the use of PI-based regimens predicted poorer adherence. The adherence rate in the current study is better than those reported from several low, middle and high income countries (Bhattacharya & Dubey, 2011; Kim, Gerver, Fidler, & Ward, 2014; Nyogea et al., 2015; Reda & Biadgilign, 2012; Ugwu & Eneh, 2013). This could be because of the practice of providing intensive counselling and frequent follow-up by health care workers and adherence case managers, particularly in the first month of treatment (MOH, 2009).

Higher rate of missed doses among those who did not use medication reminders highlights the well-recognized role of medication reminders for enhancing treatment adherence through behavioural change (WHO, 2013). This is particularly relevant for a setting where forgetfulness is the most common reason for missing as reported both in the present and previous studies (Biadgilign et al., 2008; Biressaw et al., 2013).

The rate of adherence was poorer among children receiving PI-based regimens. Poor palatability and adverse effects of PI-based regimens are known to contribute to poor adherence (Chandwani & Shuter, 2008; WHO, 2013), suggesting the need for more palatable treatment regimens.

The poorer adherence among those caregiver-child pairs enrolled in the same facility for treatment is contestable, as both need to be enrolled together if they are both HIV positive.

Existing stigma and discrimination against people with HIV in the studied areas (Biru, et al 2015) could be a contributing factor, as caregivers may not attend their nearby HIV clinic for fear of stigma and discrimination. This in turn may lead to missed appointments or failure to collect new medication (Reda & Biadgilign, 2012). The other reason could be due to sub-optimal care being provided to the caregivers from the facility. This may result in a decreased level of commitment towards the child's treatment (WHO, 2013).

The study has some limitations. Using the caregivers report method is likely to have overestimated the rate of adherence. Recall and social desirability biases are also a possibility. The use of prospective adherence measurement approach early in the course of the treatment is the main strength of this study.

Availing medication reminders, careful selection of ART regimens, and improving child-caregiver communication with regard to disclosure of HIV status should be emphasized in HIV programs. Further large scale study using a combination of adherence measuring methods in the beginning of treatment initiation is needed to bring forward a more convincing report in resource limited settings.

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