DOSE TIMING OF ANTIRETROVIRAL DRUGS AMONG HIV-INFECTED ADOLESCENTS IN A SUB-SAHARAN TERTIARY HEALTH INSTITUTION

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ABSTRACT

Background: *The introduction and use of antiretroviral therapy among HIV-infected persons has recorded successes when adherence is kept at a level of ≥ 95%. Studies show that adherence to the prescribed antiretroviral dose timing is an important factor in achieving this success. The aim of the study was to determine the proportion of HIV-infected adolescents adherent to prescribed dose timing, assess the level of difficulty to adherence to dose timing and identify factors associated with adherence to dose timing of prescribed antiretroviral therapy medications.*

Methods: *A prospective study design was used to carry out the study in Abuja, Nigeria. Each enrolled adolescent was followed up for 6 months at two monthly intervals.*

Results: *Results from 135 adolescents aged 10 to 19 years were analysed. Majority were males 73 (54.1%), aged 10 to 13 years (n= 76; 56.3%) and Christians (n = 102; 75.6%). One hundred and four (77.03%) adolescents had never had a problem with taking their drugs while 94% were adherent to their scheduled dose timing medication. There was a weak association between adherence to dose timing and the age of the adolescent (p= 0.043 OR= 4.08 CI 0.69-23.2).*

Conclusion: *The proportion of adolescents adherent to dose timing was high. Majority did not have a problem with taking their ARV medications. It is recommended that dose timing adherence of scheduled ARV medications be assessed routinely along with other adherence measures as studies have shown its importance in viral load suppression and prevention of drug resistance.*

Key words*: dose timing; antiretroviral, adherence, HIV-infected, adolescent.*

INTRODUCTION

Nigeria is the second leading country globally after South Africa with the highest burden of HIV[1]. With improving access to antiretroviral (ARV) therapy, more HIV-infected children are growing into adolescents. However, an adherence level of ≥ 95% is generally accepted as a requirement for the success of ARV therapy for HIV-infected persons because of the ability of the virus to multiply and mutate rapidly[2]. Therefore, HIV-infected persons on ARV medications need to be adherent in order to prevent drug resistance, frequent hospitalisation and poor quality of life[3,4]. Medication adherence is defined as "the ability of the person living with HIV/ AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and immune

function"[5] meaning the extent to which a person's behaviour in taking prescribed medications agrees with the recommendations of a healthcare provider[5].

Most studies on adherence to ARV medication have assessed adherence by measuring proportion of doses taken with very few studies assessing adherence to scheduled dose timing. Studies have shown that non adherence to dose timing or medication schedules for ARV drugs can have a negative effect. Delayed dosing and the subsequent subtherapeutic drug levels can lead to viral resistance and treatment failure while early dosing may on the other hand cause supratherapeutic drug levels and toxicity[6].

Patients who take their ARV drugs on time have three times less HIV in their blood than those who allow three hours before or after the designated time[7]. Also, dose-timing errors can be responsible for the virological outcomes that arise from assessing only missed doses during adherence assessments[8].

Unfortunately, adherence to dose-timing is not commonly assessed in studies. Adherence is commonly assessed (especially in resource-poor settings using patient self-report and pill count. The aim of this study was to determine the proportion of HIV-infected adolescents adherent to ARV medication dose timing, the level of difficulty to medication adherence and identify factors associated with adherence to dose timing.

METHODOLOGY

This was a prospective study carried out at University of Abuja Teaching Hospital, Gwagwalada, Abuja, Federal Capital Territory (FCT). The data collection was over a one year period from September 2015 to August, 2016.

The study population comprised adolescents aged 10 years to 19 years attending the PSTC, who had been on ARV medication for a minimum of six months and whose caregivers had given written consent if the adolescent was less than 18 years or individual consent if the adolescent was aged 18 or 19 years. Verbal assent was also obtained from adolescents less than 18 years old. Adolescents who were mentally challenged at the time of the study or who had temporary enrollment at the clinic at the time of the study were excluded.

One hundred and forty-five adolescents were enrolled into the study. However, only results from 135 (93.1%) adolescents were used as 10 (7.4%) were lost to follow up. Convenience sampling method was used because of the limited number of HIV-infected adolescents attending the clinic.

Each adolescent was assessed four times: at enrolment, at 2 months, at 4 months and at 6 months. Two-monthly interval was used for the participants convenience as clinic and pharmacy refill appointments were 2 monthly while 6 months end follow up period was used because of the expected undetectable viral after 6 months of adherence to ARV therapy[9].

A pretested questionnaire developed by the researcher was used to obtain information on socio-demography and dose timing. Blood for CD4 count and viral load were drawn and analysed using a PARTEC cyflow counter for

CD4 count and Tachmann 96, Roche Amplicor assay for viral load which reads undetectable when the viral load is less than or equal to 20 copies/ ml.

Administration of questionnaires was via a face to face interview. The responses were filled in by the researcher or a trained assistant to try to ensure completeness and understanding of the questions. For confidentiality, participants' names and other means of identification were not entered into the questionnaire, only identification numbers assigned by the researcher were used. Self-report of dose timing of ARV medication use by the participant in the 3 days prior to presentation at the clinic was assessed. Participants were asked the number of times they were supposed to take their medications in a day. All participants were on twice daily (morning and evening) medications. They were then asked what time the medication was to be taken each day and what time the participants took the medication. Any ARV medication not taken within two hours of the agreed time (one hour before or 1 hour after) was taken as a missed dose[10]. Dose timing was assessed using the formula: Number of doses taken at the prescribed time/ Number of doses prescribed multiplied by 100. A level of ≥ 95% was assessed as adherent and less than 95% as non adherent.

Data analysis was done with SPSS version 20. Frequency tables were used to express proportions. Chi square and logistic regression were used to determine associations between the independent variable (adherence to dose timing) and dependent variables (age, gender, marital status, social class, administration of medications, religion, disclosure, caregiver status, educational status, CD4 count and viral load) after categorizing the dependent variables. $P < 0.05$ was regarded as statistically significant and confidence interval (CI) was calculated at 95%. Analysis of social class was based on the classification by Olusanya *et al*[11].

Ethics approval for the study was obtained from the Health Research and Ethics Committee of the University of Abuja Teaching Hospital before commencement of the study.

RESULTS

Socio-demographic distribution of adolescents

One-hundred and forty-five adolescents were enrolled into the study. However, results of 135 were analysed as 10 (6.7%) did not complete the study giving a response rate of 93.1%. These included 73 (54.1%) males and 62 (45.9%) females with a male to female ratio of 1.18:1. The adolescents were aged 10 year to 19 years. The mean age was 13.15 years with standard deviation of ±2.436. Majority of the adolescents were in their early adolescence, 10 – 13 years (n= 76; 56.3%). Forty-seven (34.8%) were in the Junior Secondary School (JSS) classes while 55 (40.7%) belonged to the middle social class. Table I shows the socio-demographic distribution of the adolescents.

Table 1: Socio-demographic distribution of the adolescents

Variables	Males n (%)	Females n (%)	Total n (%)
Age			
10 – 13 years	38 (28.2)	38 (28.2)	76 (56.3)
14 – 16 years	29 (21.5)	19 (14.1)	48 (35.6)
17 – 19 years	6 (4.4)	5 (3.7)	11 (8.2)
Total	73(54.1)	62 (45.9)	135 (100)
Level of education of adolescents	1 (0.7)	1 (0.7)	2 (1.5)
	43 (30.4)	44 (31.1)	87 (61.5)
Tertiary	29 (21.5)	17 (12.6)	46 (34.1)
Secondary			
Primary			
Social class			
Lower	20 (14.8)	15 (11.1)	35 (25.9)
Middle	34 (25.2)	21 (15.6)	55 (40.7)
Upper	19 (14.1)	26 (19.3)	45 (33.3)

Responsibility of administering ARV drugs

The ARV drugs were mostly administered by both the caregivers and study participants working together (n=59 43.7%). The least group had only the study participants as the sole administrator of the drugs (n=27; 2%). This is depicted in Fig 1.

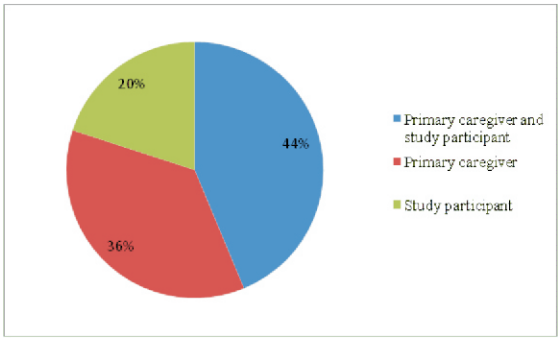

Fig. 1: Responsibility of administering antiretroviral drugs

Assessment of level of difficulty in taking ARV drugs

One hundred and four adolescents (77%) reported that taking their ARV drugs was "never a problem". Only one (0.7%) adolescent reported that taking their medication was "almost always a problem". The level of difficulty with taking ARV drugs is depicted in Table 2.

Table 2: Assessment of difficulty in taking ARV drugs

Level of difficulty	n	Percent (%)
Never a problem	104	77
Hardly ever a problem	22	16.3
Frequently a problem	8	5.9
Almost always a problem	1	0.7
Total	135	100

Adherence to dose timing

The adherence level to dose timing among the adolescents in the first, second, third and fourth visits were 92.6%, 93.3%, 88.1% and 88.1%, respectively giving an average of 94.1%.

Association between adherence to dose timing and variables

Adherence to dose timing was higher in adolescents who were less than 15 years (n= 102; 75.6%) compared with adolescents who were ≥ 15 years (n=25; 18.5%). This was significant using Chi square at p = 0.043 but not significant when logistic regression was applied (OR: 4.08, CI: 0.69-23.2). There was no statistical significant association between adherence to dose timing and; gender, marital status of primary caregiver, social class, administration of medication, religion, disclosure, biological or non-biological primary caregiver, educational status, CD4 count and viral load. This is shown in Table 3.

Table 3: Association between adherence to dose timing and variables.

Variable	Adherent (%)	Non adherent (%)	Odds ratio (CI)	P value
Age of adolescent				
< 15 years	102 (75.6)	4 (3)	4.08(0.69-23.2)	0.043
...	25 (18.5)	4 (3)		
Gender				
Female	71 (52.6)	2 (1.5)	3.8(0.64-39.56)	0.089
Male	56 (41.5)	6 (4.4)		
Marital status of caregiver				
Married	81 (60)	3 (2.2)	2.93(0.538-19.6)	0.942
Single (single, separated, divorced)	46 (37)	5 (3.7)		
Social class				
Upper	44 (32.6)	1 (0.7)	2.54 (0.19- 136.2)	0.220
Middle	52 (38.5)	3 (2.2)		
Lower	31 (23)	4 (3)	5.68 (0.52- 285.8)	
Administration of medications				
PC§1	48 (35.6)	1 (0.7)	1.85(0.02-147)	0.176
SP§2	26 (19.3)	1 (0.7)	5.43(0.62-255.01)	
PC§1 and SP§2	53 (39.3)	6 (4.4)		
Religion				
Christian	97 (71.9)	5 (3.7)	1.94(0.28-10.6)	0.376
Muslim	30 (22.2)	3 (2.2)		
Disclosure				
Yes	**49 (36.3)**	**2 (1.5)**	**1.88(0.32-19.73)**	0.442
No	**78 (57.8)**	**6 (4.4)**		
Caregiver				
Biological	100 (74.1)	5 (3.7)	2.22(0.32-12.19)	0.284
Non biological	27 (20)	3 (2.2)		
Educational status of PC				
No formal	7 (5.2)	1 (0.7)	1(0.011-89.9)	0.693
Primary	7 (5.2)	1 (0.7)	0.41(0.029-24.7)	
Secondary	51 (37.8)	3 (2.2)	0.33(0.023-20.3)	
Tertiary	62 (45.9)	3 (2.2)		
CD4 count (cells/mm^3)				
<500	44 (32.6)	2 (1.5)	1.59 (0.31 –8.21)	0.577
≥500	83 (61.5)	6 (4.4)		
Viral load (cells/mm^3)				
≤20	74 (54.8)	5 (3.7)		
>20	53 (39.3)	3 (2.2)	0.84 (0.19- 3.66)	0.814

§1= Primary caregiver §2= Study participant

DISCUSSION

Adherence to dose timing among the adolescents was higher than that reported in studies carried out in Ethiopia[12], South Africa[10], Sweden[13], and China[14]. The difference could be from the differences in methods in carrying out these studies such as the sample populations as three of these studies[11,13,14] were among adults while one[10] was among children aged less than seven years old. The study in Ethiopia among 105 adults applied a mixed-method study design[11]. That in South Africa was a longitudinal study among 53 caregiver/child dyads and assessed liquid formula ARV medications using Medication Event Monitoring Systems (MEMS) for 46 of the children[10]. The sample size of 53 however, may be too small to draw conclusions[10]. The authors also noted that although MEMS assessed dose timing better than some other methods, the use of MEMS was quite expensive and so not affordable for regular use in resource-limited settings[10]. The study carried out in Sweden used a cross sectional study design similar to this study but their self-administered questionnaire assessed a four day recall for dose timing[13]. The sample size was slightly larger than this study but it was among adults. Gill *et al*[14] in the study in China, used a longitudinal observation study design with a sample size of 69 adults selected with convenience sampling method. Dose timing was assessed using Electronic Drug Monitor (EDM) which may be another reason why the adherence level was lower compared with this study that used self-report. The use of self-report has been reported to overestimate adherence[15,16,17]. A major weakness is that they are prone to bias as assessment is based on patient recall and honesty although they have the advantage of being less costly and questionnaires can be

flexible[18].

The high adherence level to dose timing in this study was corroborated with the report by the adolescents using a likert scale that most of them had never had a problem with taking their ARV medication.

The association between dose timing and age was significant using chi square but not significant with logistic regression analysis. Adolescents less than 15 years were more adherent to ARV drugs. This could be because the younger adolescents are more likely to have their caregivers involved in administering their ARV drugs unlike the older adolescents who may be left on their own as their caregivers may feel they are old enough to take on that responsibility solely[19]. A study with a larger sample size may be required to show a significant association if any exists. Mukhtar –Yola *et al*[20] reported that 85% of the study participants took their medications on time. However, no analysis was done to associate dose timing with other factors or variables. Haberer *et al*[21] did not assess dose timing because of the controversies surrounding the contribution of dose timing to viral suppression. However, an association was seen between dose timing and large pill burden in another study[13]. The adults in the study were three times less likely to be adherent if taking 10 or more pills in a day (OR = 3.656 CI: 1.918 – 6.969)[13]. While Gill *et al*[14] in yet another study reported that adherence to dose timing using EDM, showed the highest likelihood to accurately predict the patients who would have undetectable viral load and also showed the strongest statistically significant association between dose timing using EDM and undetectable viral load when compared with measuring proportion of doses taken with EDM (P = 0.03, OR = 7.8 CI: 1.0 67.4), measurement using pill count (P = 0.51) and measurement with self-report visual analogue scale (P = 1.0). The finding in that study in China[14] is different from the observation in this study where the association between dose timing and viral load was not statistically significant. The difference may be due to the measurement instrument. This study relied on a three day self-report while the other study used electronic drug monitoring. This study supports the paucity of available data on the importance of assessing dose timing during adherence assessment of patients. There was paucity of data to compare association of dose timing with the other factors assessed in this study suggesting the need for more studies on dose timing to be carried out.

A limitation of this study is the convenience sampling method used to select participants as the results obtained may not be generaliseable to all adolescents in Nigeria. A random sampling method of sample selection would have been preferred. The use of an electronic drug monitor, MEMS or a direct method of measuring adherence such as ARV drug assays may have been better in assessing adherence as self-reports have been showed to overestimate adherence levels. However, these devices are not readily available in the locality and are quite expensive. Their regular use in clinics will not be feasible.

CONCLUSION

Adherence to scheduled dose timing of ARV medications among the adolescents was high and majority did not have any problem taking their medications. Adherence assessment to

dose timing should not be neglected as studies have shown its importance in viral load suppression and prevention of drug resistance which will in turn lead to better health outcomes and improved quality of life of HIV-infected persons.

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