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Original Research Article

Adherence to antiretroviral therapy and factors affecting adherence among paediatric HIV patients

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ABSTRACT

Background: Adherence to antiretroviral therapy (ART) is the strongest indicator of successful treatment of Human Immunodeficiency Virus (HIV) among children. The main aim of the present study was to know the prevalence of adherence at our centre and various factors affecting the adherence in children.
Methods: It was an observational study done in children less than 15 years of age, affected with HIV. 78 children attending Paediatric Centre of Excellence (PCOE) for HIV L.T.M.G. Hospital, Sion, Mumbai were included in study, Study period was 18 months from January 2012 to June 2013. Complete history of the patients was noted in a pre-designed proforma. Baseline investigations related to HIV were done in all children. Fixed dose combination ART was started in children who fulfilled clinical and/or immunological criteria as per the NACO guidelines. Adherence was estimated using Pill count method. All the data were analysed by using 10.0 version of statistical software SPSS.
Results: In this study, male children (57.7%) out numbered the females (42.3%). Majority of study subjects were more than 10 years of age. Overall adherence among subjects was 82.1% at the end of one year and non-adherence was 17.9%. There was no significant association of age and gender of the patients with adherence ($p>0.05$). Education, employment and knowledge towards medication of care takers was significantly associated with adherence of ART ($p<0.05$). Adherence of study cases had not showed any significant association with ART treatment regimen ($p=0.99$). At the end of one year, the mean CD4 count was significantly more as compared to baseline among adherence group and the mean CD4 count was significantly less as compared to baseline among non-adherence group. The most common reason for missed dosage was forgot to take medicine in 29 subjects (37.1 %).
Conclusions: Adherence level in this study was good. Forgot to take the medicine was the main reason given by the patients for non-adherence. Education, employment and knowledge towards medication of care takers was significantly associated with adherence of ART. But further studies are needed to explore various other factors related to adherence in children.

Keywords: Antiretroviral therapy, Adherence, Paediatric HIV patients

INTRODUCTION

The human immunodeficiency virus (HIV)/Acquired Iimmunodeficiency Syndrome (AIDS) pandemic remains the most serious of infectious disease challenges to public health. Globally, an estimated 35.3 million people are living with HIV. Of them, 3.3 million were children living with HIV worldwide while in India 2.1 million people are living with HIV 0.2 million are children.[1] Advances in Antiretroviral medications have resulted in

decline in morbidity and mortality amongst HIV infected patients. However high levels of adherence is required for the success of ART.[2]

Adherence of at least 95 % is needed for patients on ART to keep the viral load undetectable levels for as long as possible and to maintain the functionality of the immune system

Sustained adherence requires a consistent supply of medications along with education and support.[3] Government of India has tried to remove the structural barriers for accessing ART by its free ART roll-out programme and a network of link centres. But poor adherence to ART is still seen leading to suboptimal ART regimens, resulting in rapid development of drug resistance.[4,5]

Several methods have been developed for measurement of adherence that includes DOT (Directly observed therapy), therapeutic drug monitoring (TDM), medication event monitoring system (MEMS), self-report and Pill counts.[6] In pill count method, adherence is usually calculated by counting the remaining doses of medication and assuming that the remaining pills in excess of what is expected to represent missed doses.[7]

In literature, very few studies are available depicting factors related to adherence in children, so study was undertaken with the aim to determine the prevalence of adherence to ART amongst HIV infected patients on ART and to determine the factors lead to adherence and non-adherence to ART.

METHODS

This was an observational prospective cohort study conducted at Paediatric Centre of Excellence (PCOE) for HIV care at L.T.M.G. Hospital, Sion, Mumbai from January 2012 to June 2013.

Written informed consent was taken from all patients. The study was approved by ethics committee of the medical college. A total of 78 HIV diagnosed children less than 15 years of age from January 2012–June 20123 were included in the study. All patients were followed up for 1 year.

Study design

Children attending Paediatric Centre of Excellence (PCOE) for HIV care were recruited in the study. All children enrolled were assigned a study number. History including demographic details and clinical symptoms as well as examination was noted in a pre-designed proforma. For socioeconomic class estimation modified Kuppuswamy's classification was used.[8]

Baseline investigations were done that included a complete blood count, absolute CD4 lymphocyte count and percentage, liver and kidney function tests, various investigations to rule out tuberculosis such as Erythrocyte sedimentation rate, chest radiograph, tuberculin test (considered positive if the induration was more than 5 mm) and ultrasonography of abdomen to look for evidence of retroperitoneal lymph nodes and/ inter loop ascites.

Other relevant investigations for various opportunistic infections such as cytomegalovirus, Toxoplasmosis, Pneumocystis Jerovecii pneumonia, cryptococcosis, Mycobacterium avium complex etc. were done as indicated in a given child. These investigations enabled us to stage the child clinically as per WHO classification.[9] CD4 counts were done at baseline and were repeated at 6 monthly intervals.

Fixed dose combination ART was started in children who fulfilled clinical and/or immunological criteria as per the NACO guidelines.[10] The fixed dose combinations used were: ZLN (Zidovudine+Lamivudine+Nevirapine), ZLE (Zidovudine+Lamivudine+Efavirenz), SLN (Stavudine+ Lamivudine+Nevirapine), SLE (Stavudine+ Lamivudine+Efavirenz), ZL LPV/r (Zidovudine+ Lamivudine+lopinavir/ritonavir) and SL LPV/r (Stavudine+Lamivudine+lopinavir/ritonavir).

All caretakers of patients underwent two counselling sessions prior to starting on ART. All caretakers were counselled regarding importance of adherence. Counselling was reinforced on every monthly follow up visit.

Pill count method was used to estimate adherence. Adherence was calculated by dividing the number of pills actually taken by a given patients to the number of pills that were supposed to be taken by him over 1 month period.

Adherence was checked on each monthly follow up visit. Those patients with adherence more than 95% were considered as adherent and those with less than that as non-adherent i.e. poor adherence and all patients were asked about the reason for missing dose.

Statistical analysis

In this study, all the data were analysed by using 10.0 version of statistical software SPSS. Continuous variables were summarized by using summary statistics (number of observations, mean and standard deviation) and categorical values by using frequencies and percentages. For all study cases, descriptive statistics were estimated and presented in tables to know the overall profile.

In this study, percentage of adherence was compared with gender, education of caretaker, employment status, socioeconomic status and clinical stage by using Chi square test.

Average % CD4 levels were compared between adherent and non-adherent subjects by using student's t test. All values were reported based on two-sided and all the statistical tests were interpreted at 5% level of significance level.

RESULTS

Table 1 shows that 57.7% of the study subjects were male and 42.3% were female. Majority of study subjects were more than 10 years of age (41.0 %).

Table 1: Profile of age and gender (n=78).

Age group (years)	Gender				Total	
	Male		Female			
	No.	%	No.	%	No.	%
<1	08	17.8	06	18.2	14	17.9
1-5	10	22.2	04	12.1	14	17.9
5-10	08	17.8	10	30.3	18	23.2
>10	19	42.2	13	39.4	32	41.0
Total	45	57.7	33	42.3	78	100.0

Figure 1 depicts that at the end of one month of starting ART, 59.0% of the cases were adherent while at the end of 7 month, 70.5% of the cases showed adherence and at the end of one year overall adherent subjects were 82.1%. At the end of one month 41.0% of the cases showed non-adherence and at the end of 7 months 29.5% of the cases showed non-adherence and at the end of one year 17.9% of the cases showed non-adherence.

Table 2 presents the association of adherence with age and gender of the patients. At 1 year of follow up, adherence was better in children between 1-5 years of age (100%) as compare to other age groups, but the difference was not statistically significant.

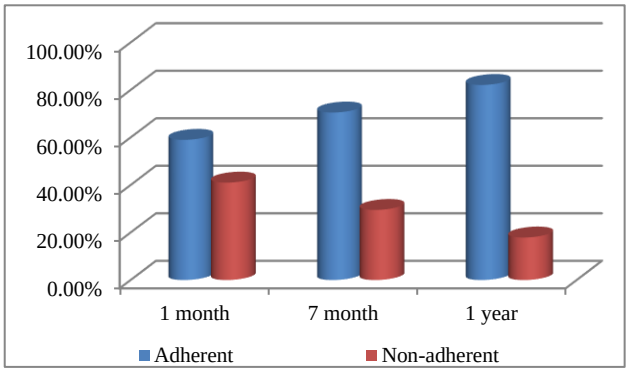

Figure 1: Profile of percentage of adherent and non-adherent case at various time points.

Table 2: Association of adherence with age, gender of the study participants after 1 year follow up.

Age group (years)	Adherence at 1 year follow up				Total		P value
	Adherent		Non-adherent				
	No	%	No	%	No	%	
< 1	11	78.6	03	021.4	14	100.0	
1-5	14	100.0	-	-	14	100.0	
5-10	15	83.3	03	016.7	18	100.0	0.232
> 10	24	75.0	08	025.0	32	100.0	
Total	64	57.7	14	042.3	78	100.0	
Gender							
Female	26	78.8	07	21.2	33	100.0	0.520
Male	38	84.4	07	15.6	45	100.0	

Children who had biological parents there were more adherent to ART as compared to children with others as caregivers. Children whose caretakers were educated were more adherent than those who were not. 75.4% of the study subjects whose caretakers were unemployed were adherent which was significantly less as compared to 100% of the cases who had employed caretaker. All the cases that had upper and middle-class caretakers were adherent which was more as compared to among those whose caretaker were belonging to lower socioeconomic status. Caretakers who had knowledge of medication at start of ART were adherent (97.1%) which was more as compared to (69.8%) those not having knowledge of medication and this difference was statistically significant

(p 0.02). Study group cases who belonged to clinical stage 4 had 54.6% adherence which were low as compared to 83.0 -90.0 % among those belonging to stage 1, 2 and 3 but the difference was not significant (p=0.097) as given in Table 4.

Table 3: Association of general characteristics of caregivers with patients and adherence at 1 year follow up.

Caretaker's characteristics		No. of cases (N = 78)		Adherent		Non- adherent		P value
				No	%	No	%	
Relation ship								
Biological parents	Father	26	61 (78.2)	25	96.2	01	03.8	0.115
	Mother	35		28	80.0	07	20.0	
Others	Grand parents	09	15 (19.2)	06	66.7	03	33.3	
	Uncle/aunt	06		04	66.7	02	33.3	
NGO		02	02 (02.6)	01	50.0	01	50.0	
Education								
Illiterate		09		04	44.4	05	55.6	0.05
Primary/secondary/high school		57		48	84.2	09	15.8	
College/university		12		*12	100.0	-	-	
Employment								
Employed		21		21	100.0	-	-	0.016
Unemployed		57		*43	75.4	14	24.6	
Economic class								
Upper/middle upper middle		06		06	100.0	-	-	0.181
Middle lower middle		09		09	100.0	-	-	
Lower lower/lower upper lower		63		49	77.8	14	22.2	
Knowledge of medication								
Doesn't know		43		*30	69.8	13	30.2	0.02
Knows		35		34	97.1	01	02.9	

Table 4: Association between clinical stage of HIV and adherence at 1 year follow up.

Clinical Stage	No. of cases (n=78)	Adherent		Non-adherent	
		No	%	No	%
		09	90.0	01	10.0
2	12	10	83.3	02	16.7
3	45	39	86.7	06	13.3
4	11	06	54.6	05	45.4

Table 5: Association between ART regimen and adherence at 1 year follow up.

ART regimen	No. of cases (n=78)	Adherence at 1 year follow up			
		Adherent		Non-adherent	
		No	%	No	%
SL LPV/r	04	03	75.0	01	25.0
SLE	10	08	80.0	02	20.0
SLN	08	07	87.6	01	12.4
ZL LPV/r	11	09	81.8	02	18.2
ZLE	19	15	79.0	04	21.0
ZLN	26	22	84.6	04	15.4

Out of 78 cases, 64 cases showed adherence with ART regimen and 14 cases showed non-adherence to ART regimen (p=0.99). There was no significant association of ART regimen with adherence Those study subjects who were taking other medications beside ART were adherent in 65.5% cases which was low as compared to 91.8% who did not take other medications besides ART and difference was significant as given in Table 6. Table 7 presents the mean change in percentage of CD4 counts in children of below and above 5 years of age.

In children below 5 years of age the mean baseline CD4 percentage in adherent group was less as compared among non-adherent group but the difference was not significant. At the end of 7th month and 1 year, mean CD4 count among adherent group was significantly more as compared to baseline and the mean CD4 count among non-adherent group was significantly less as compared to baseline.

Table 6: Association between medications besides ART and adherence at 1 year follow up.

Medication besides ART	No. of cases (n=78)	Adherence at 1 year follow up			
		Adherent		Non-adherent	
		No	%	No	%
No	49	*45	91.8	04	08.2
Yes	29	19	65.5	10	34.5

In case of children above 5 years of age the mean baseline CD4 count among adherent group which was significantly less as compared non-adherent group. At the end of 7th month and 1 year, the mean CD4 count among adherence group was significantly more as compared to baseline whereas the mean CD4 count among non-adherence group was significantly less as compared to baseline.

Table 7: Changes in mean CD4 counts among children below and above 5 years age group.

Duration	Children <5 years of age		Children >5 years of age	
	Mean CD4% ($\overline{X}$ ± SD)		Mean CD4% ($\overline{X}$ ± SD)	
	Adherent (n = 64)	Non-adherent (n = 14)	Adherent (n = 64)	Non-adherent (n = 14)
1 month	29.55±15.70	35.87±09.91	427.23±375.30	646.45±859.08
7 months	*34.14±13.65	*26.50±05.63	*694.18±415.41	402.64±435.31
1 year	*35.44±12.03	*24.67±04.62	*905.44±413.74	439.91±380.55

By Student 't' test- P<0.05, *Significant.

Figure 2 shows the reasons for poor adherence. About 29 study subjects (37.1%) revealed the reason for missed dosage as forgot to take the medicine.

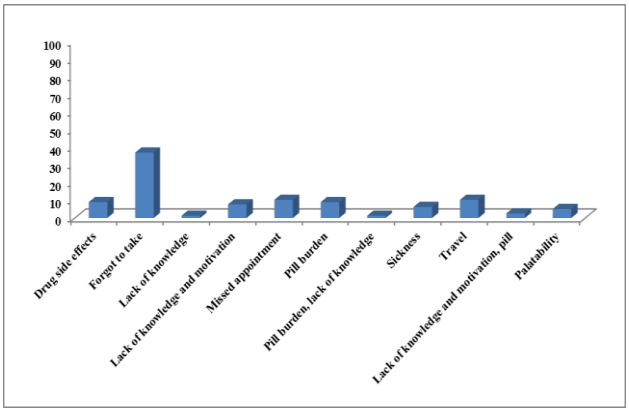

Figure 2: reason for missed dosage.

DISCUSSION

Adherence to ART is very crucial in order to maximize the benefit of the drugs and prevent resistance development. The benefits of ART include increased survival, improvement of immunity, prevention of development of opportunistic infections, improved quality of life, and promotion of growth and development. Inadequate adherence is associated with immunological, virological failure, drugs resistance and treatment failure.[11]

In this study, overall adherence in our centre at 1 year follow up was 82.1% and non-adherence was 17.9%. Our study results correlate with other similar studies.[12-14] This high percentage of adherence might be due to regular follow up by patients and adherence counselling done at each follow up visit thereby enabling patients to adhere better.

Adherence counselling and duration of ART had great influence on adherence. In our study, 59% study subject were adherent after 1 month of starting ART which significantly increased after 7 months (70.5%) and after 1 year (82.1%) of starting ART. Several studies indicated that adherence may vary over time. Gallant et al showed that as adherence tends to wane after the first month on antiretroviral therapy, special intervention around the end of the first month on therapy should improve long-term adherence.[15] Indian cohort study by Beck et al found that duration of treatment for less than 6 months or greater than 10 years was associated with the largest number of

missed doses and life time adherence to ART was statistically significantly associated with regular follow-up attendance.[16]

In our study, we did not find statistically significant association between adherence and age, gender and socioeconomic class of caretakers. This was consistent with the study by Venkatesh et al who showed that demographic characteristics, such as age, gender, occupation, and residential status, did not predict treatment adherence.[17] In this study, education of caretaker (p=0.005) and employment (p=0.016) was positively associated with adherence. Higher education level was associated with better understanding regarding ART regimens and effective counselling was possible in them. This was consistent with the study by Murphy et al who observed that being in school was associated with better adherence.[18]

In the present study, clinical stage of HIV was not statistically relating to adherence (p=0.097), although we found adherence to be low in subjects with stage 4 of HIV as compared to stage 1, 2 and 3. Some studies described an increased adherence in those with the history of opportunistic infections. This shows that prior opportunistic infections increased adherence suggesting that illness severity motivated patient's adherence.[19]

Caretakers who had good knowledge of medication were adherent (97.1%) as compared to those lacking it (69.8%) (p=0.002). Similar observations were also noticed by De Bruin et al.[20]

In our study, use of various different ART regimens had no impact on adherence (p=0.990). This was in accordance with findings of Fong et al.[21] In contrast, Laniece et al found that the type of drug combination influences adherence.[19] We did not find any association between ART regimens with adherence, but we found association between adherence and medication side-effects that were experienced within the last month. In a study of adherence to ART in Botswana, Weiser et alfound that 9% of the cohort reported missing doses due to side-effects.[22] In our study 9% of study subjects experienced side effects due to drugs that caused them to miss some doses of drugs.In our study we observed that those study subjects who were taking medications in addition to ART were less adherent (65.5%) as compared to (91.8%) subjects who were taking only ART (p=0.05).

Our study findings showed that CD4 count or percentage significantly improved in those study subjects who were adherent and decreased in non-adherent subjects (p=0.05). Limitation of our study was non-availability of viral load testing at our center so we used CD4 level as predictor of response to ART.

The most common reason (in 29% study subjects) mentioned by caretakers for missing doses was forgetfulness. Several other studies also revealed the main reason accounted for non-adherence as patients simply forgetting to take ART and having a busy schedule.[23,24] This factor is responsible for non-adherence was subsequently minimized with adherence counselling regarding reminder tools in subsequent follow up visits.

One of the factors identified by De Bruin et al to non-adherence was a lack of motivation.[20] We found non-adherence due to lack of motivation in 10.3% study subjects. One Indian cohort study showed that medication adherence increased by 100% in those on less than 5 tablets per day.[16] In contrast to this, previous study of Rakmanina reported that despite having the new regimens, fewer tablets and daily doses, adherence still remains a problem.[25] We also found good adherence with lesser pill burden. Pill burden in 9% cases led to non-adherence.

CONCLUSION

Adherence to ART will result in HIV durable viral suppression, improvement in CD4 cells, reduced rates of resistance, increased survival, and improved quality of life of HIV infected children. Further studies are needed to explore various other factors related to adherence in children.

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