AIDS Behav (2016) 20:1076–1083
DOI 10.1007/s10461-015-1207-7

ORIGINAL PAPER

Adherence to Antiretroviral Therapy Among Children Living with HIV in South India

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Published online: 6 October 2015

Abstract Adherence to ART, fundamental to treatment success, has been poorly studied in India. Caregivers of children attending HIV clinics in southern India were interviewed using structured questionnaires. Adherence was assessed using a visual analogue scale representing past-month adherence and treatment interruptions >48 h during the past 3 months. Clinical features, correlates of adherence and HIV-1 viral-load were documented. Based on caregiver reports, 90.9 % of the children were optimally adherent. In multivariable analysis, experiencing ART-related adverse effects was significantly associated with suboptimal adherence ($p = 0.01$). The proportion of children who experienced virological failure was 16.5 %. Virological failure was not linked to suboptimal adherence. Factors influencing virological failure included running out of medications ($p = 0.002$) and the child refusing to take medications ($p = 0.01$). Inclusion of drugs with better safety profiles and improved access to care could further enhance outcomes.

Keywords Adherence · Children · HIV · Antiretroviral therapy · Virological failure

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Background

The HIV epidemic continues to have devastating consequences globally, and its effects are magnified among children who are infected. According to WHO global estimates, a total of 34 million people are living with HIV, of which 3.3 million are children less than 15 years of age [1]. Based on HIV sentinel surveillance 2008–2009, it is estimated that India has 2.4 million people living with HIV, of which 3.5 % are children. Following the launch of the national pediatric antiretroviral therapy (ART) initiative by India's National AIDS Control Organization in November 2006, nearly 106,824 children living with HIV in India were registered in HIV care at ART centres, of whom less than half, 42,105 children were receiving ART as of March 2014 [2].

ART has been shown to markedly improve the health of HIV-infected children. It has been found to reduce plasma HIV RNA levels, increase CD4 counts, decrease the incidence of opportunistic infections and improve the growth and development of children [3, 4]. An important factor in achieving treatment success is maintaining optimal adherence to ART. Studies both in adults [5, 6] and children [7, 8] have demonstrated that achieving and maintaining a high level of adherence is essential for successful viral suppression by ART. Prospective studies have shown that risk of virological failure increases as the proportion of missed doses increases [9–11]. Further, sub-therapeutic antiretroviral drug levels resulting from poor adherence may facilitate the development of drug resistance to one or more drugs in a given regimen, as well as possible cross-resistance to other drugs within the same class [12, 13]. Therefore, in addition to compromising the efficacy of the existing regimen, suboptimal adherence has the potential to limit future effective drug regimens for patients who

develop drug-resistant viral strains. Transmission of drug resistant virus within the community can impact public health adversely by reversing the gains achieved from wide scale ART access.

Although optimal viral suppression ideally requires an adherence rate of 95 % and above [9], reported adherence estimates among children range from 50 to 80 %, with estimates in the upper end of this range reported from lower-income settings [10, 14]. Due to the paucity of data examining the factors associated with adherence among HIV-infected children in India, particularly in the context of the recent scale up of pediatric ART using generic fixed-dose combination pills (FDCs) [2], this study was undertaken to measure the level of adherence, determine the correlates and barriers of adherence, assess factors associated with virological failure, and examine the association between adherence and virological failure among HIV-infected children in south India.

Methods

Study Population and Sites

This was a questionnaire-based cross-sectional study involving face-to-face structured interviews of the caregivers of children recruited for the study. HIV-infected children younger than 18 years and their caregivers attending the ART centres at two tertiary care institutions in south India; St. John's Medical College Hospital in Bangalore, and Indira Gandhi Institute of Child Health in Bangalore, were invited to participate in this study between October 2011 and March 2013. Recruitment occurred on clinic days during the study period at the respective ART centres. If there was more than one child in a family, the child on ART or the older child was included in the study. Children received ART as per the national guidelines [15]. Before initiation of ART, the caregiver received 2–3 separate counseling sessions that covered various aspects of care including ART therapy, adherence, nutritional needs, psychosocial needs, possible consequences of low adherence, possible adverse events and ways to address them. Children who had received ART for over 6 months were considered ART-experienced and eligible for participation in the study.

Ethical Considerations

Ethical clearance was obtained from the respective Institutional Ethical Review Boards at each institution. Written informed consent was taken from the parents or legal caregivers willing to participate in the study. All patients were given standard clinical care and counseling as per the national guidelines [15].

Data Collection

Data were obtained using a structured questionnaire, which was administered to the caregivers by trained research staff at the respective ART centre. To encourage unbiased reporting by caregivers and children, the interviews were conducted by trained non-medical personnel who were not associated with their medical care. Participants were assured of confidentiality, and caregivers were assured that their children's present disclosure status would be maintained. Demographic characteristics such as age, sex, residence, education, socioeconomic status, child HIV disclosure and caregiver HIV status were obtained by asking the caregiver directly. Medical information such as WHO clinical stage, recent CD4 count and percentage (within the previous 3 months) and viral load measurements were obtained from the medical charts. Using the structured questionnaire, barriers to adherence such as patient-specific or caregiver-related factors, medication-related factors, and health care delivery factors were explored.

Adherence Measurement by Self-report

Caregivers were asked to describe their child's ART regimen, to report on the number of missed doses per day during the past 3 months, and whether there were any treatment interruptions for greater than 48 h over the last 3 months. A visual analogue scale (VAS) to indicate the percentage of medications taken during the previous month was also used [16]. Possible strategies that caregivers had used to improve adherence were listed, and caregivers endorsed the ones they employed.

Definitions

Optimal adherence was defined as adherence >95 % in the past month, based on the VAS measure [9]. Those who reported lower levels of adherence were classified as sub-optimally adherent. Treatment interruptions were defined as having missed ART for >48 h anytime within the past 3 months [10]. Virological failure was defined as plasma HIV-1 viral load >400 copies/ml [7]. Disclosure was considered as 'full' when it involved the caregiver having disclosed to the child that he or she has HIV specifically, while the term 'partial disclosure' was used when the illness was described in a way that was consistent with HIV, although the term 'HIV' was avoided. The term 'no disclosure' was used when the caregiver reported telling the child nothing about his or her illness [17].

Statistical Analysis

Descriptive statistics consisted of frequency tabulations for categorical variables, and means and standard deviations (SD) for continuous variables. Associations between suboptimal adherence/virological failure and other categorical variables were tabulated in two-way frequency tables, and significance of the association tested via the Chi square test. For continuous variables, means were compared between those with optimal and suboptimal adherence, and those with and without virological failure. The significance of the differences in means between the groups was assessed via *t* test. Multivariable logistic regression analysis of variables that were significantly associated with suboptimal adherence and with virological failure in bivariate analyses was performed. All *p* values reported were two-sided and values <0.05 were considered statistically significant. Analyses were performed using Stata version 13.

Results

Patient Characteristics

Between October 2011 and March 2013, 247 caregiver-children dyads participated in our study. Among the caregivers, 60 % were biological mothers of the respective child, 15 % fathers and the remaining were legal guardians or extended relatives who were the primary caregivers. There were 164 children who were ART-experienced for at least 6 months, and were eligible for inclusion in the analyses reported here. In general, children consumed two pills a day, consisting of the fixed dose combination of zidovudine, lamivudine and nevirapine. All these children were perinatally infected. Mean age among the ART-experienced children was 10.2 years (SD $\pm$ 3.6) and with 58.0 % males. A total of 75 % of the children were in early stages (WHO clinical stage 1 or 2) of their illness at the time of interview. Mean duration on ART was 36.7 months (SD 22.8 months).

ART Adherence

Of the 164 children on ART, caregivers reported that 149 (90.9 %) children were optimally adherent, and 15 (9.1 %) suboptimally adherent. Only 8 (4.9 %) caregivers reported any treatment interruptions in the children's ART of greater than 48 h in the past 3 months. The socio-demographic and clinical characteristics of children in both groups of optimal and suboptimal adherence were not significantly different (Table 1). The proportion of children who had full disclosure of their HIV status was 12.2 %.

Factors Associated with ART Adherence

Individual or Interpersonal Factors

We found that all the caregivers had received counseling at their respective centers, as per recommendations laid down by the national guidelines [15]. Although most children had not undergone HIV disclosure, we found that among the 20 children with full disclosure who were on ART, none of the respective caregivers reported suboptimal adherence. Unwillingness to medicate the children in front of others was found to be a significant interpersonal barrier to adherence (OR 3.15; 95 % CI 1.06–9.37; $p = 0.03$) on bivariate analysis although statistical significance was lost when adjusted for other factors in multivariable analysis (Table 2).

ART or Medication-Related Factors

Most children were either on zidovudine or stavudine based regimens, and we did not find any association of adherence with the type of regimen the child was on. The duration on ART did not show any relation to the reported adherence, but experiencing ART-related adverse effects was significantly associated with suboptimal adherence; 2 % of those with optimal adherence, compared with 13.3 % with suboptimal adherence experienced ART-related adverse effects (OR 7.48; 95 % CI 1.14–48.91; $p = 0.01$). In adjusted analysis of all factors influencing adherence, we found that experiencing adverse effects of ART remained independently associated with suboptimal adherence (OR 14.01; 95 % CI 1.87–104.64; $p = 0.01$) (Table 2).

Health System Related Factors

Among factors related to health systems, participants listed 'running out of medications', 'inconvenient visiting clinic hours', 'difficulty paying for transportation to the clinic', and 'finding it physically tiring to reach the clinic' as potential deterrents to adherence. On bivariate analysis, we found that 'running out of medications' (OR 5.23; 95 % CI 1.55–17.62; $p = 0.004$) was significantly associated with suboptimal adherence. This statistical significance was however lost on multivariable analysis (Table 2).

Factors Associated with Virological Failure

Among the children on ART, 16.5 % were found to be in virological failure. The age and sex of the child was not associated with virological failure ($p = 0.79$ and 0.06 respectively). The distribution of virological failure was similar among children who were suboptimally and

Table 1 Characteristics of children on ART, categorized by optimal and suboptimal adherence

Parameter	Optimal adherence, n = 149 (%)	Suboptimal adherence, n = 15 (%)	*p*
Age			
≤10 years	74 (49.6)	7 (46.6)	0.82
Sex			
Male	84 (56.3)	11 (73.3)	0.20
Household income			
<80 US $	68 (45.6)	8 (53.3)	0.52
Caregiver education level			
No formal education	34 (22.8)	6 (40.0)	0.18
Primary school	29 (19.5)	4 (26.7)	
Middle school and above	86 (57.7)	5 (33.3)	
Clinical			
Advanced (WHO stages 3 and 4)	37 (24.8)	2 (13.3)	0.31
Mean CD4 percentage ± SD	26.82 ± 9.64	25.22 ± 14.14	0.67

WHO World Health Organization, *SD* standard deviation

Table 2 Factors related to adherence to ART: n (%)

Parameter	Optimal adherence, n = 149 (%)	Suboptimal adherence, n = 15 (%)	Odds ratios	
			Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
Individual/interpersonal factors				
Did not want to medicate in front of others	48 (32.2)	9 (60.0)	3.15 (1.06–9.37)*	2.67 (0.78–9.06)
Was away from home	45 (30.2)	7 (46.6)	2.02 (0.69–5.91)	
Forgot to take medication	31 (20.8)	5 (33.3)	1.90 (0.60–5.97)	
Child refused medications	21 (14.1)	4 (26.7)	2.21 (0.64–7.61)	
ART related factors				
Zidovudine-based ART	49 (32.8)	5 (33.3)	1.19 (0.37–3.86)	
ART duration ≥2 years	99 (66.4)	8 (53.3)	0.54 (0.18–1.58)	
Experienced ART-related adverse effects	3 (2.0)	2 (13.3)	7.48 (1.14–48.91)**	14.01 (1.87–104.64)**
Health system related factors				
Had difficulty paying for transportation to clinic	67 (44.9)	10 (66.7)	2.44 (0.79–7.5)	
Physically tiring	48 (32.2)	8 (53.3)	2.40 (0.82–7.01)	
Ran out of medications	13 (8.7)	5 (33.3)	5.23 (1.55–17.62)**	3.94 (0.94–16.49)
Felt that visiting clinic hours were inconvenient	6 (4.0)	1 (6.6)	1.70 (0.19–15.16)	
Clinical correlate				
Experienced virological failure	23 (15.4)	4 (26.7)	1.97 (0.57–6.74)	1.39 (0.33–5.86)

* $p < 0.05$; ** $p \leq 0.01$

optimally adherent (26.7 and 15.4 %, respectively; OR 1.97; 95 % CI 0.57–6.74; $p = 0.26$) (Table 2). We found that those children with lower CD4 percentages were more likely to experience virological failure ($p = 0.04$). Virological failure was not significantly related to the duration on ART, ART regimen, adverse effects of ART or full disclosure of HIV status. In bivariate analysis, we found that the child refusing to take medicines (OR 3.75;

95 % CI 1.44–9.74; $p = 0.004$), running out of medications (OR 7.05; 95 % CI 2.47–20.11; $p < 0.001$) and caregivers finding it physically tiring to reach the ART centers (OR 2.89; 95 % CI 1.24–6.72; $p = 0.01$) were significantly associated with virological failure. However, only running out of medications (OR 7.28; 95 % CI 2.07–25.56; $p = 0.002$) and the child refusing to take medications (OR 3.82; 95 % CI 1.30–11.19; $p = 0.01$) retained statistical significance on multivariable analysis (Table 3).

Caregiver Strategies for Optimal Adherence

Caregivers used different strategies as reminders to administer medications on time. Over 50 % maintained written records of medications administered, and almost all of them reported that they would carry extra medications when they travelled. Other strategies used included the use of pillboxes and alarm reminders (Fig. 1).

Discussion

Our study found that the proportion of children whose caregivers reported optimal adherence of ≥95 % in the past month was 90.9 %. Despite such high reported rates of ART adherence, 15.4 % of these optimally adherent children did not achieve virological suppression. Experiencing adverse effects was significantly associated with adherence to ART, while running out of medications and refusal of the child to take medications were factors significantly associated with virological failure.

Adherence rates reported in other studies from diverse settings have ranged from 50 to 80 %, with the upper range of estimates reported from lower-income settings [10, 14]. Several factors may have contributed to the high rate of self-reported adherence in our setting. Reporting bias and over-estimated self-report of adherence by caregivers is well known [14], and could have contributed towards higher values seen in our setting. Moreover, the reported past-month adherence reflects a relatively short window of time, and may not take into consideration adherence levels in the past months and years of ART. Other factors such as the provision of comprehensive healthcare services free of cost, a deep emphasis on counseling, higher overall awareness levels about HIV medications, and the use of various strategies to improve adherence could have contributed to higher rates of adherence. Most children were also on a simple twice-a-day low pill-burden regimen, which has been earlier reported to be associated with better adherence to ART in children [18].

Our findings of adherence not being related to the age and gender of the child are in agreement with reports from other studies [7, 18]. Despite several children being on

Table 3 Factors related to virological failure n (%)

Parameter	VL < 400, n = 136 (%)	VL > 400, n = 27 (%)	Odds ratios	
			Unadjusted OR (95 % CI)	Adjusted OR (95 % CI)
Individual/interpersonal factors				
Fully aware of HIV status	15 (11.0)	5 (18.5)	1.83 (0.60–5.55)	
Did not want to medicate in front of others	46 (33.8)	11 (40.7)	1.34 (0.57–3.13)	
Was away from home	45 (33.1)	7 (25.9)	0.70 (0.27–1.79)	
Forgot to take medication	32 (23.5)	4 (14.8)	0.56 (0.18–1.75)	
Child refused medications	16 (11.7)	9 (33.3)	3.75 (1.44–9.74)**	3.82 (1.30–11.19)**
Suboptimal adherence to ART	11 (8.1)	4 (14.8)	1.97 (0.57–6.74)	1.03 (0.22–4.82)
ART related factors				
Zidovudine-based ART	43 (31.6)	10 (37.0)	1.25 (0.52–2.98)	
ART duration ≥ 2 years	85 (62.5)	21 (77.7)	0.86 (0.38–1.92)	
Health system related factors				
Had difficulty in paying for transportation to clinic	63 (46.3)	14 (51.8)	1.24 (0.54–2.85)	
Physically tiring	41 (30.1)	15 (55.5)	2.89 (1.24–6.72)**	1.29 (0.66–2.52)
Ran out of medications	9 (6.6)	9 (33.3)	7.05 (2.47–20.11)***	7.28 (2.07–25.56)**

n = 163 as viral load was not done for one

* $p < 0.05$; ** $p \leq 0.01$, *** $p \leq 0.001$

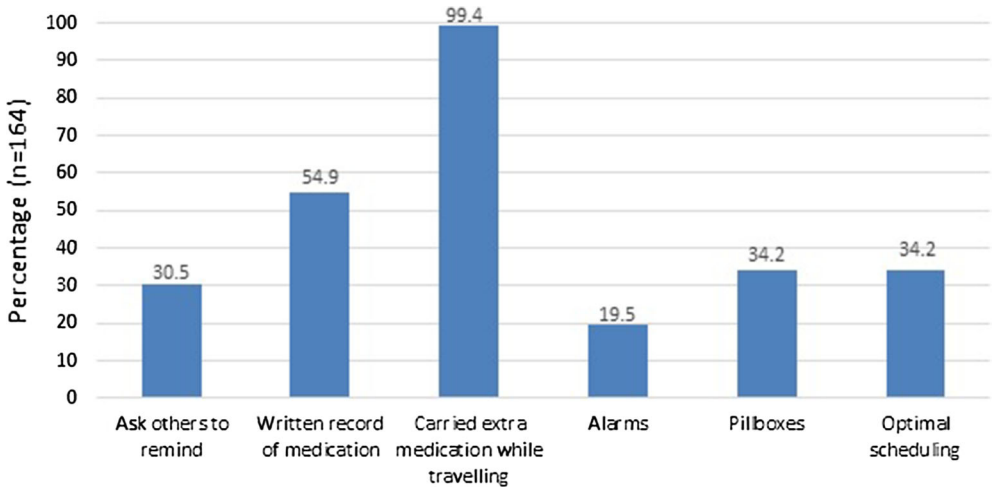

Fig. 1 Strategies used by the caregiver for improving adherence

ART for durations exceeding 2 years, they do not seem to have demonstrated treatment fatigue, and we did not find any correlation between the duration on ART and the level of adherence.

The child's reported ART adherence is strongly influenced by the caregiver's and family's level of functioning, which may change over time [14]. While the physical role of the caregiver in terms of administering ART diminishes as the child grows older, the need for psychological support from the caregiver remains crucial at every age. Caregiver cognitive ability has earlier been shown to correlate with adherence [19], and caregivers' lower levels of education and perceived difficulty with ART administration have been demonstrated to be negatively associated with adherence in studies from USA and Togo [20, 21]. In our study, a majority of caregivers had received formal education for longer than 8 years, and this might have contributed to high rates of adherence we observed. Many caregivers often undertook various measures to ensure that adherence was maintained, and these measures also seem to have contributed to higher rates of adherence that we report. Some studies from high-income settings have shown that disclosure was associated with worse adherence [22, 23]. However, the combined evidence from a recent review of disclosure of HIV status among children in resource limited settings has suggested that disclosure may play an important role in improving medication adherence and HIV-related outcomes [24]. In our study, we found that among the children with full disclosure, none of the respective caregivers reported suboptimal adherence.

We found that caregivers of those children who experienced adverse effects of ART were more likely to report poor adherence. These findings are in agreement to those reported by other authors earlier [25, 26]. It has been suggested that safer and simpler regimens, which minimize adverse effects, are desirable for achieving optimal adherence [27]. The stigma surrounding HIV infection has been known to further complicate the management of children living with HIV [25]. In our study, we found that unwillingness by the caregivers to medicate children in front of others also contributed to suboptimal adherence, although the significance was lost on multivariable analysis.

Running out of medication supplies was found to be significantly associated with poor virological outcomes, underlining the impact of challenging access to healthcare as a potential deterrent to optimal outcomes in such children. Several caregivers in our study reported that they had to travel for long durations, found it physically tiring and had difficulty paying for transportation to reach the provider facility. Other studies, from north India, have reported a strong relationship of poor adherence with the distance travelled to reach the ART center and the travel cost [25, 27]. The study period saw the launch of the link worker scheme under the third phase of the National AIDS Control Program [2], aiming to address HIV prevention and care needs of high risk and vulnerable groups in rural areas. Expansion of the scope of such schemes to enhance outreach, along with task shifting to nurse-based and home-based care may help to address some of these issues.

Among the children on ART in our study, we found that 15.4 % had virological failure despite reported optimal adherence. Although several studies describe the close link between adherence and viral suppression [28–30], the potential reasons for the non-correlation of adherence and viral load could be manifold. First, the adherence measurement tool used in this study only covered the previous month and hence may not have reflected long-term adherence. Second, previous non-adherence or other factors such as using a failing regimen and presence of drug

resistance can also result in detectable viral load despite recently reported near-perfect adherence [30–32]. Third, reporting bias is well-known with self-reported adherence information [14]. In addition to sustained adherence (thereby resulting in optimal therapeutic drug levels), several factors, including gender of the child, lower CD4 counts, longer duration on ART [33], genetic variants [34], co-infection with tuberculosis and lower baseline weight [35] have all been demonstrated to affect virological suppression. Some of these factors were not significant in our study, and therefore factors influencing virological failure in such settings of relatively high adherence need further study.

This study has certain limitations, the most important of which is recall bias. Self-reports from caregivers and patients often tend to overestimate adherence. The caregivers may have been prone to a desirability bias, responding positively, but not entirely accurately, to the research staff. The non-clinical staff who administered the questionnaires in our study were not involved in routine clinical care and may have overcome this limitation to some extent. The cross-sectional design can also be a limitation, in that it precludes causal interpretations. Additionally, the fact that the study had only 15 children with caregiver-reported suboptimal adherence limited the power of the study and on statistical analyses led to wide confidence intervals for some variables as well. Further, the study was restricted to only two centers in one state of south India—since adherence factors are usually contextual, this precludes generalization of the results to other regions in India. A larger multi-site study would likely yield data more representative data for India.

Conclusion

In conclusion, we report that caregiver-reported adherence to ART among children attending these ART centers under the national AIDS control program in India is high. Challenges to achieving optimal adherence and virological outcomes include ART related adverse effects and difficulties in accessing provider facilities. Emphasis on access to care, inclusion of ART drugs with better safety profiles and provision of community-based services could further improve overall outcomes in pediatric HIV.

Acknowledgments The authors would like to acknowledge the staff at Indira Gandhi Institute of Child Health, Bangalore and the ART Centre, St. John's Medical College Hospital for their excellent teamwork and patient care. We would also like to thank the study team for their outstanding efforts in recruiting and interviewing the children and caregivers. We are grateful to the National AIDS Control Organization (NACO), Government of India, for providing support for these participants, and to the Karnataka AIDS Prevention Society (KSAPS) for facilitating the conduct of this study. Most importantly, we are grateful to the study subjects for participating in this study. We gratefully acknowledge grant support from the National Institute of Mental Health, Bethesda, MD, USA (Grant R01MH067513) awarded to MLE; and the Wellcome Trust-Department of Biotechnology India Alliance Senior Fellowship awarded to AS (IA/S/13/2/501017).

Author's Contributions Conceived and designed the study: AS MLE GNS. Performed the experiments: AS GNS. Analyzed the data: EH AS MLE KM. Wrote the paper: KM AS MLE EH.

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