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► **To cite this version:**

Karthikeyan Paranthaman, Nagalingeswaran Kumarasamy, Devaleenol Bella, Premila Webster. Factors influencing adherence to Anti-Retroviral Treatment in children with Human Immunodeficiency Virus in South India - A qualitative study. *AIDS Care*, 2009, 21 (08), pp.1025-1031. 10.1080/09540120802612857 . hal-00545373

HAL Id: hal-00545373

<https://hal.science/hal-00545373>

Submitted on 10 Dec 2010

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**Factors influencing adherence to Anti-Retroviral Treatment
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Journal:	<i>AIDS Care - Psychology, Health & Medicine - Vulnerable Children and Youth Studies</i>
Manuscript ID:	AC-2008-06-0262.R1
Journal Selection:	AIDS Care
Keywords:	Pediatric HIV, ART, Medication adherence, Interventions, India



Journal Name in Full

Vol. X, No. X, Month 200X, 000–000

ARTICLE TYPE [ORIGINAL ARTICLE]

Article Title [Factors influencing adherence to Anti-Retroviral Treatment in children with Human Immunodeficiency Virus in South India - A qualitative study]

Abstract

The aim of the study was to gain a deeper understanding of the factors that influence adherence to ART in a paediatric population in South India. Semi-structured interviews, guided by a questionnaire based on literature review, were undertaken with fourteen primary caregivers of children with HIV on ART focusing on the factors influencing adherence and non-adherence. Adherence to ART was assessed by caregiver reported adherence for the last three days. The framework approach was used for analysis of the transcribed interviews. Adherence behaviour in children taking ART was influenced by medication, child, caregiver, family and healthcare service related factors. Medication related factors such as palatability, formulation, and difficult regime were among the common reasons for non-adherence. While a supportive family appears to contribute to adherence, some caregivers are reluctant to inform their family for fear of isolation. All participants were strongly appreciative of the study centre's model of care and this had a positive effect on adherence behaviour. From the public health point of view, the respondents' reluctance to access publicly funded HIV care services is a cause for concern. Almost all caregivers were sceptical of the quality of free ART medications provided by public services, indicating an urgent need for appropriate education to

alleviate their concerns. The cost of ART was reported by caregivers as an important barrier, particularly by those with low income. Most caregivers recommended wider access to free ART, availability of child-friendly medications and adherence counselling as important interventions to improve adherence. All caregivers in this study reported some difficulty in sustaining adherence in their children. Further research on improving adherence in children by tailoring interventions to the specific needs of caregivers and their families is warranted.

Keywords: Paediatric HIV; ART; medication adherence; interventions; India

Title Page Footnote:

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MANUSCRIPT**Introduction**

Anti-Retroviral Treatment (ART) for Human Immunodeficiency Virus (HIV) infection in children has dramatically improved survival and quality of life. However the effectiveness of ART is dependent on good adherence (Paterson et al., 2000).

Sustaining good adherence to ART in children is difficult as it is influenced by several factors including child behaviour, tolerability of medications, access to health services, HIV status of caregivers and their attitudes and beliefs (Bikaako-Kajura et al., 2006; Boni, Pontali, De Gol, Pedemonte & Bassetti, 2000; Elise et al., 2005; Giacomet et al., 2003; Gibb et al., 2003; Goode, McMaugh, Crisp, Wales & Ziegler, 2003; Hammami et al., 2004; Marhefka, Tepper, Brown, & Farley, 2006; Martin et al., 2007; Mellins, Brackis-Cott, Dolezal & Abrams, 2004; Nicholson et al., 2006; Pontali et al., 2001; Reddington et al., 2000; Temple, Koranyi, & Nahata, 2001; Williams et al 2006). Non-adherence leading to anti-viral resistance necessitates the use of more expensive and often more toxic second or third line drugs with disastrous implications at both individual and population levels (Mullen et al., 2002). Attaining the highest level of adherence is therefore crucial in children.

Although studies have been published on the epidemiology of HIV and effectiveness of ART among Indian children (Madhivanan et al., 2003; Merchant, Oswal, Bhagwat & Karkare, 2001; Pensi, 2007; Natu & Daga, 2007), there is no literature on the factors

influencing adherence in Indian children. The aim of this qualitative study was to gain an insight into adherence behaviour and the factors that affect adherence in children, as reported by caregivers.

Methods

Qualitative research is best suited to explore and understand the beliefs, values and processes underlying behavioural patterns of adherence and non-adherence in the caregiver (Sankar, Golin, Simoni, Luborsky & Pearson, 2006). Methods used in qualitative research include direct observation, interviews, analysis of texts or documents and recorded speech or behaviour. Among these methods, in-depth interviews are preferable as they can elicit people's experiences and views in their own words, reveal new areas not anticipated at the start of the study and permit exploration of individual's perceptions and beliefs (Britten, 2006). This technique does not use pre-set questions, but is shaped by a defined set of topics. The topics (Table 1) were informed by a literature review of published studies relevant to factors influencing adherence in children (Bikaako-Kajura et al., 2006; Boni et al., 2000; Elise et al., 2005; Giacomet et al., 2003; Gibb et al., 2003; Goode et al., 2003; Hammami et al., 2004; Marhefka et al., 2006; Martin et al., 2007; Mellins et al., 2004; Nicholson et al., 2006; Pontali et al., 2001; Reddington et al., 2000; Temple et al., 2001; Williams et al 2006). All interviews were conducted by the principal investigator who had no role in the clinical care provided at the organisation. Baseline characteristics of the caregiver and child were recorded. As reported adherence in the last three days has been proven to predict virologic response in

children (Van Dyke et al., 2002), the caregiver was asked about adherence of the child and if applicable, themselves. If the child (and caregiver) had not missed any dose of medication in the last three days, he/she was considered to be adherent. If any dose was missed he/she was considered non-adherent. Semi structured interviews with a loose structure and open-ended questions defining the area to be explored were initially used. During the interview, the researcher diverged from the questions to pursue particular ideas and responses in more detail.

Participants

A convenience sample of fourteen caregivers responsible for routinely administering ART to the child (or children) attending a non-profit medical care and research institution based in Chennai, India between May and June 2007 participated in the study. Children under twelve years on ART for at least three months were included. Those on prophylactic medication were excluded. Written informed consent was obtained following explanation of the study. Participants were offered a nominal sum of hundred rupees (~\$2.50). The sample size of fourteen was determined by time constraints and non-emergence of new themes (data saturation) as the interviews progressed.

Analysis

All interviews were translated to English and transcribed by an independent agency to reduce bias and cross-checked for accuracy by the principal investigator. The transcripts

were imported to NVivo version 7 (©QSR International Pty. Ltd, Doncaster, Australia). As the objectives of the investigation are set in advance and based on the information requirements of the researcher rather than emerging from a reflexive research process, the framework approach was used for analysis (Pope, Ziebland & Mays, 1999). The analytic process consisted of five stages – familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation.

Results

The baseline characteristics of the caregivers and their children are summarised in Table 2 and 3. The results are presented under the main topic headings.

1. Medication related factors

Medication related factors that influence adherence are mainly associated with side effects, size of tablets, palatability and tablet regime. Some children complained about the taste of the medicines.

“Sometimes he will cry about the bitter taste of the medicines and it takes a lot of effort to make him take it.” (L – caregiver of non-adherent child)

ART medication is often required to be taken twice-daily and this caused a few problems.

“There is a chance of missing the night dosage when they go to bed earlier. If I wake them up to give the medicines, they will cry and refuse to take the medicines.” (J – non-adherent caregiver of adherent child)

The need for weight based dosage in children and the lack of syrup formulations meant caregivers found it difficult to give the medication as it was difficult to break the tablets into exact doses.

“Once they prescribed 1/3rd of the tablet but it is difficult to give. For this, syrup would have been better. I feel it is difficult because we are unable to break the tablet correctly. I have the feeling that I am not giving the correct dosage.” (F – adherent caregiver of adherent child)

Some caregivers expressed fears about adverse effects and interaction of medicines.

“While giving the ENT medicines (antibiotics), I stopped the ART medicines. I was concerned my child might get side effects while taking ENT medicines (with ART).” (D – adherent caregiver of adherent child)

“I have a fear in my mind that he may get side effects as I have been giving him medicine since childhood.” (F – adherent caregiver of adherent child)

2. Child related factors

Child related issues such as willingness to take medications, refusal and disclosure were suggested by caregivers as factors significantly affecting adherence.

“Even if I forget to give the medicines, my younger son will remind me. As soon as he finishes his meal, he will ask for the tablets.” (L – caregiver of non-adherent child)

“Sometimes when he goes to sleep, it’s hard to wake him up and give the medicines. On occasions, he will (deliberately) spill the medicines”. (B – non-adherent mother of adherent child)

None of the children in the study were aware of their illness. All caregivers admitted they worried about disclosure and its implications as their children got older.

“We are getting tense about this. When he was young, there was no problem. Now that he is getting older, he is asking lot of questions.” (L – caregiver of non-adherent child)

Fears about disclosure combined with hopes of HIV cure in the near future may act as a facilitator for adherence.

“When she grows up, we have to tell her why she needs to take these medicines. I wish she gets cured before we come to that stage. That's why I am giving these medicines regularly.” (G – adherent caregiver of adherent child)

3. Caregiver/family related factors

Most of the participants felt that supportive and affectionate families were an important factor in enabling adherence.

“When I am away, my parents are usually at home. They are aware of the HIV status, so we tell them to give the tablets.” (M – caregiver of adherent child)

“I don't have a stable life since my husband is a difficult person. Sometimes he would not even let me take the medicines by creating a lot of problems. That's the reason why tablets get missed.” (I – adherent caregiver of non-adherent child)

While some participants had disclosed the nature of the illness to other family members and were able to get their help, others were afraid to let other members of the family know about the illness.

“My mother-in-law lives with us. She is unaware of this disease. Everyone won't have the same opinion and accept the child. Suppose if they ignore the child, it would affect the child more. For the sake of the child we didn't reveal to anybody.” (F – adherent caregiver of adherent child)

“I don’t know for how many years I am going to live so I have disclosed this to my parents. My in-laws are elderly and they won't be able to cope with this. I have also explained to my parents about the medicine regime of my children. Someone else has to know, isn't it? If something happens to us, they have to look after our children.” (A –adherent caregiver of adherent child)

The majority of caregivers felt HIV was no worse than other diseases such as cancer.

“According to the society HIV is a terrible disease, but as far I am concerned we also live like other normal people. Compared to this, cancer is even more terrible.” (J – non-adherent caregiver of adherent child)

Non-disclosure of HIV status meant that caregivers used a variety of strategies to encourage children who refused medication, to convince them to adhere. Several caregivers felt that gentle persuasion was often effective. However a couple of caregivers admitted that they sometimes had to use physical force.

“I would let him to play with toys and go outside for a ride. When he gets satisfied he would listen to our words. In this way, I convince him to take the medicines.” (N– caregiver of adherent child)

“I have to beat him. And he will take the medicines for the fear of beatings.” (L– caregiver of non-adherent child)

Participant’s perceptions of their child’s future varied widely with some being positive about their children’s future while others had a gloomier outlook.

“I have a strong belief that by continuing the medicines my child’s future will not get affected.” (H – caregiver of adherent child)

“When they get older, they have to marry. This disease affects all that. I am worried about their future. No matter how much medicines I give, I feel bad that my children may not be able to marry and lead a normal life like others.” (I – adherent caregiver of non-adherent child)

4. Healthcare service related factors

Most participants were reluctant to use public healthcare services due to stigma and concerns about confidentiality as HIV services are usually situated within a main hospital with other clinical services.

“I cannot get my medicines from government hospitals as it is in the public area. Some other people from my town may come to government hospitals. I do not mind spending money to come here as no one else knows about this.” (J – non-adherent caregiver of adherent child)

The caregivers’ perception of quality of free medications was linked to their trust and confidence in the health services providing them. Almost all caregivers raised concerns about the quality of free ART provided in public hospitals

“I don’t believe government will give good-quality medicines for free.” (C – adherent caregiver of adherent child)

The relationship between healthcare providers and caregivers appeared to influence adherence.

“All the staff in this hospital will enquire whether we are taking the medicines properly and coming regularly for check-up. Since they care so much about us, it’s our duty to adhere to treatment responsibly.” (A – adherent caregiver of adherent child)

5. Other factors

The economic status of the family was an important determinant in adherence behaviour due to the cost of ART.

“If we had to pay for our medicines, it’s not possible for us (to buy the medicines). Then we had to stop these medicines altogether.” (B – non-adherent caregiver of adherent child with a household income of Rs.2000 (\$50))

However, some caregivers with high household income were hesitant to get free ART as they perceived it would have an impact on the quality of medicines.

“When we started, it used to cost Rs.800 (\$20). Now it has come down to Rs.500 (\$12.50). If the cost comes down, quality also comes down. Then there is no point in giving (poor quality) medicines.” (M – caregiver of adherent child with household income >Rs 5000(\$125))

“I would prefer to pay for the medicines. I have fear about the quality of medicines because this boy is the most important in our family and he has to remain healthy.” (L – caregiver of non-adherent child who had lost both parents, income not disclosed.)

Access to free ART medicines, child-friendly formulations and adherence counselling were the important interventions recommended by caregivers to improve adherence (Table 4).

“I don’t think there is any other major factor apart from the cost of medicines. If medicines are made available, then taking them is not an issue” (D – adherent caregiver of adherent child)

“The size of the tablet can be reduced, tablets taken once on daily basis will be better or the medicines can be provided in a liquid syrup formulation.” (A – adherent caregiver of adherent child)

“The doctors should instruct the parents that the medicines should be given correctly. Through counseling the doctors have to explain that there are many benefits from taking the medicines.” (K – adherent caregiver of adherent child)

Discussion

The results of the study illustrate that adherence to ART in children is a complex phenomenon and sustaining adherence presents unique challenges to caregivers, their families and healthcare providers.

Medication related factors such as palatability, formulation, and difficult regime were among the common reasons for non-adherence. These findings are consistent with earlier studies. (Boni, et al, 2000; Giacomet et al., 2003; Gibb et al., 2003; Goode et al, 2003; Martin et al., 2007; Pontali et al., 2001; Temple et al, 2001). While improving access to child-friendly formulations is vital, the use of simplified regimen, fixed dose combinations and less frequent dosing requirements, coupled with educating caregivers on the benefits and side effects of ART may also improve adherence (WHO, 2006; Working Group on Antiretroviral Therapy and the Medical Management of HIV-Infected Children, 2006).

Child related factors appeared to be less important compared to other factors. From a caregivers' perspective, the study revealed an unmet need for support and guidance from health services regarding disclosure to the child. While a supportive family appeared to

contribute to adherence, some caregivers are reluctant to inform their family for fear of isolation. Interventions to educate and encourage family members to support each other need to be explored in future research. None of the children were aware of their illness and caregivers admitted they worried about disclosure and its implications as their children got older. When the child refused to take medication, caregivers used a variety of strategies with a small minority admitting that children were beaten to force adherence. Appropriate counselling and support to caregivers is vital to prevent such behaviour. Most caregivers felt that wider access to free ART, availability of child-friendly medications and adherence counselling were the most important interventions to improve adherence.

All participants were strongly appreciative of the study centre's model of care (YRG CARE, Undated) and this had a positive effect on adherence behaviour. From the public health point of view, the respondents' reluctance to access publicly funded HIV care services is a cause for concern. Policy makers need to take into account the views and needs of caregivers to ensure that HIV care services are confidential, free of stigma and comprehensive. Almost all caregivers were sceptical of the quality of free ART medications provided by public services, indicating an urgent need for appropriate education to alleviate their concerns.

The cost of Art was reported by caregivers as an important barrier, particularly by those with low income. In the absence of free ART, many caregivers would be unable to afford the costs of treatment resulting in non-adherence. Previous studies in India among adults

arrived at similar conclusions (Gupta & Shankar 2004; Kumarasamy et al., 2005; Safren et al, 2005). In recent years, India has made remarkable progress in providing free ART, particularly in high-burden areas. However access to free ART remains an issue for a significant proportion of HIV infected people. Interestingly two caregivers in our study preferred to pay for the medications citing concerns about the quality of free medications. While this implies a need for interventions to improve trust among patients about the quality of free ART, it also suggests that a means-tested approach for access to free ART might be a feasible option, although this needs to be explored in a larger study.

The limitations of this study must be noted. The study included a non-representative sample of fourteen Tamil-speaking caregivers, who have a common socio-cultural lifestyle, in a non-profit institution providing HIV services exclusively and therefore, the sample may not be representative of the entire cohort of caregivers of HIV infected children in India. Assessment of adherence was ascertained by caregiver report.

Although caregiver reported adherence has been validated by previous studies (Van Dyke et al., 2002), it is possible that participants might have reported an overestimated level of adherence.

Despite these limitations, this study is the first to evaluate the adherence behaviour of caregivers of children taking ART in India. The results provide useful information for improving clinical practice and public policy. All caregivers in this study reported some difficulty in sustaining adherence in their children. Further research on improving

adherence in children by tailoring interventions to the specific needs of caregivers and their families is warranted.

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Acknowledgements:

We would like to express my sincere gratitude to all participants in the study for sharing their experiences with us. The authors would also like to thank the staff at YRG CARE for their help and support in the conduct of this study. The principal investigator would like to gratefully acknowledge his wife Monira for her invaluable comments and proof-reading the manuscript.

For Peer Review Only

Table 1. Interview guide for topics covered in the in-depth interview**(To be placed in the middle of ‘Methods’ section)**

-
1. Medication related factors - taste, formulation, regime, side effects
 2. Child related factors – willingness to take medications, disclosure
 3. Caregiver/family related factors - family support, perceptions and attitude towards HIV
 4. Healthcare service related factors - confidentiality, quality of care
 5. Other factors – cost of ART, adherence interventions
-

Table 2: Characteristics of primary caregivers (To be placed at the beginning of ‘Results’ section)

Variable	Number (n=14)	
Age	20-29 yrs	3
	30-39 yrs	7
	>40 yrs	3
Gender	Male	4
	Female	10
Relation to child	Mother	8
	Father	3
	Step-parent	1
	Grandparent	1
Monthly household income	<1000 rupees (\$25 approx)	5
	1000-3000 rupees (\$25 -\$75 approx)	4
	>5000 rupees (\$125 approx)	5
Education	Secondary (age11-14)	4
	Higher Secondary (age15-16)	5
	Graduate	4
HIV status	Positive	10
	Negative	4
On ART	Yes	10
	No	4
Self-reported adherence ^a	Adherent	8
	Non-adherent	2

^a n=10 for this category

Table 3: Characteristics of children taking ART (To be placed at the beginning of 'Results' section)

Variable		Number (n=14)
Age	<4 yrs	1
	4-8 yrs	5
	8-12 yrs	8
Sex	Male	11
	Female	3
ART regime ^a	AZT+3TC + NVP	5
	AZT+D4T+ NVP	5
	AZT+ D4T+EFV	4
Duration of ART	<12 months	2
	12-36 months	4
	>36 months	8
ART funding	Free	10
	Paid	4
Any parent deceased	None	8
	One	5
	Both	1
Siblings with HIV	Yes	3
	No	11
Caregiver reported adherence	Adherent	12
	Non-adherent	2

^aAZT – Zidovudine, D4T – Stavudine, EFV – Efavirenz, NVP – Nevirapine, 3TC –

Lamivudine,

TABLE 4: Adherence interventions recommended by participants (To be placed at the end of ‘Results’ section).

-
- Access to free ART
-
- Availability of child-friendly medications:
 - Once daily dosage
 - Fixed dose formulations
 - Improving the palatability
 - Syrup formulation
-
- Adherence counselling:
 - To improve knowledge about the illness and treatment
 - To inform the benefits of adherence
 - To inform the consequences of non-adherence
 - To instill the confidence to manage HIV
-