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Adherence to antiretroviral therapy in children attending Mulago Hospital, Kampala

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Abstract

Background: Non-adherence reduces the effectiveness of antiretroviral therapy in children attending the paediatric HIV/AIDS clinic at Mulago Hospital, Kampala.

Aim: To determine the levels of adherence to HAART and identify factors associated with non-adherence.

Methods: A cross-sectional study of 170 children aged 2–18 years. Adherence to HAART was defined as taking ⩾95% of prescribed medication. It was determined using three measures: a 3-day self-report by the caregivers, clinic-based pill counts at enrolment and home-based unannounced pill counts 2–3 weeks later.

Results: The 3-day self-reported ⩾95% adherence was 89.4% (n=170). Using clinic-based pill counts, 94.1% (n=170) had ⩾95% adherence to treatment compared with only 72% (n=164) by unannounced pill counts. When the primary caregiver was the only one who knew the child's serostatus, he/she was three times more likely to be non-adherent (p=0.02, OR 3.34, 95% CI 1.14–9.82). Those who had been hospitalised twice or more before starting HAART were more likely to have ⩾95% adherence (p=0.02, OR 0.44, 95% CI 0.20–0.92).

Conclusion: The majority of children had good adherence levels when estimated by unannounced pill counts. Disclosing the child's HIV serostatus only to the primary caregiver and having been hospitalised only once or not at all were associated with poor adherence.

Introduction

Worldwide, about 2.3 million children are infected with HIV, of whom nearly 90% are in sub-Saharan Africa.[1] In 2006 alone, new infections in children under 15 years were estimated to be 530,000 (410,000–660,000) and there were 380,000 deaths.[1] It is estimated that, currently, 1600 children are infected every day by their HIV-infected mothers.[2] The high seroprevalence among women increases the HIV infection rate in children, 90% of children being infected by their mothers.[3] In Uganda, the seroprevalence of HIV is 6.2% and about 100,000 children under 15 years are infected.[4] In 2002 alone, there were about 17,050 new cases and 16,740 children below 15 years of age died.[4]

By the end of 2001, less than 30,000 people were estimated to have been benefiting from antiretroviral therapy (ART) in sub-Saharan Africa.[5] In Uganda, by the end of 2002, only an estimated 10,000 AIDS patients were receiving antiretroviral drugs (ARVs), most of them in urban centres.[6] Fortunately, the cost of ARVs is coming down and there is a positive international drive to increase accessibility in resource-limited countries. Furthermore, multiple organisations and global initiatives are

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releasing funds for ARVs in developing countries.[7] The Ugandan Ministry of Health has a policy of accelerating access to comprehensive HIV/AIDS care, with a target of 60,000 people on ARVs by 2005,[6] which was achieved and even exceeded.

The goal of ART is to reduce the viral load to undetectable levels and sustain viral suppression over a long period of time. These low levels of replicating virus reduce the risk of emergence of drug-resistant mutations. If drug doses are intermittently missed, viral mutations that confer drug resistance will emerge.[8] Sub-optimal adherence to ARVs is the most common cause of virological failure of ART regimens.[9] In addition, non-adherence to one regimen can result in viral mutations that confer virus resistance to many ARVs in the same class.[10] Resistance might necessitate changing to another, probably more expensive drug regimen, yet only a limited number of treatment options are available in developing countries. Furthermore, children have fewer treatment options than adults because of a lack of suitable formulations.[10]

Adherence is an important determinant of treatment outcome. Adult studies report undetectable viral loads in 78–84% of those who take $\geqslant$95% of their medication compared with only 45–64% of those who take between 90% and 95% of their medication.[11,12] The HIV RNA pattern in children differs from adults, probably owing to the lower efficiency of an immature immune system and a larger number of HIV-susceptible cells.[10] Despite this difference, studies in children have also shown that with $\geqslant$95% adherence, a significant percentage, 50–58%, had undetectable viral loads.[13,14] This was even higher in a recent study by LeProvost where there was very good adherence, and viral loads in all the 24 children remained at $<$100 copies/ml.[15] This level of adherence is therefore recommended for maximum benefit from ART even in children. In resource-limited settings, adherence in children is generally lower than in adults.

Because there are limited data on adherence to ARVs in children in Africa, we set out to determine the levels of adherence to HAART and identify the associated factors in children attending the paediatric HIV/AIDS clinic at Mulago Hospital, the national referral hospital.

Methods

The cross-sectional study was conducted between September 2004 and February 2005 in the paediatric HIV/AIDS clinic at Mulago Hospital. It is the largest paediatric HIV clinic in the country and at the time of the study it had about 280 children on HAART. A total of 170 children aged 2–18 years who had been taking ART for at least 1 month were enrolled consecutively. Informed consent was obtained from caregivers or the children themselves if aged $\geqslant$12 years. Only children who lived within a 20-km radius of Mulago Hospital were enrolled because they all had to have home visits. The following children were excluded from the study: those who came to the clinic without their pill boxes (because clinic-based pill counts had to be done), those who were taking ARV syrup formulation, and siblings of a child already recruited for the study.

Adherence was measured using three measures: self-report, clinic-based pill counts and home-based, unannounced pill counts. Each child was subjected to all three measures only once. Self-report was used at the time of enrolment at routine clinic visits using a structured questionnaire which was pilot-tested. The questionnaire was administered by the principal investigator or research assistant, none of whom worked regularly in the clinic. The section on adherence levels was answered by children $\geqslant$12 years who were deemed old enough to understand. They were asked whether they had missed a dose the previous day, previous 3 days and previous 7 days. For the young children and others whose

pill-taking depended entirely on caregivers, the caregivers answered the question. Immediately after the interview, clinic-based pill counts were carried out. Children were given appointments every 4 weeks and provided with only enough pills for each 4-week period. After receiving treatment, the children and their caregivers were taken home by a research nurse to identify their addresses. After a period of 2–3 weeks following enrolment, the nurses visited each child once at home on a day they were not expected. An adult was asked for the pill box and the prescription books. The pills were counted in his/her presence and then compared with the date of refill and adherence thus calculated. If no-one was at home, another unannounced visit was made.

Co-variates

Independent variables included child factors such as age, gender, disclosure of HIV serostatus to the child, social support, symptomatic HIV disease, WHO stage, number of hospitalisations before starting HAART, interference with daily life and knowledge and perception of ARVs. Caregiver factors included relationship to the child, level of education, socio-economic status, caregiver also receiving ART, correct counselling recall, whether or not the child's status had been disclosed to anyone else, shared responsibility of drug administration and knowledge, attitudes and perceptions. Drug factors assessed included the regimen, pill burden, duration of HAART, side-effects and alternative therapy use.

Statistical analysis

The sample size was calculated using the Kish and Leslie formula. Since there are no published data on adherence to ART in African children, a prevalence of 50% was used. The minimum sample size was 160 at $p<0.05$. Quantitative data were checked for completeness, sorted, coded and entered into the computer using EpiInfo version 6.04. Analysis was done using SPSS 10. For the factors affecting adherence, bivariate analysis was done with a 95% confidence interval. Pearson's χ^2 test was used to determine association between adherence and dependant variables (all variables were put in two categories). Analysis of the predictors of adherence was limited to the home-based unannounced pill counts. All variables with $p<0.2$ were entered into logistic regression analysis.

We obtained consent for the study from the Department of Paediatrics and Child Health of Makerere University, Faculty of Medicine Research Committee, the Uganda National Council for Science and Technology, and the management of the study site. The consent and assent forms were in English and translated into *Luganda*, the language commonly used in the area.

Results

A total of 170 children were enrolled and visited at home, 164 of whom had successful visits where unannounced pill counts were conducted (Table 1). Ages ranged from 2 to 18 years, with mean and median ages of 9.8 and 10 years, respectively. About 75% lived within 10 kilometres of the study site (Mulago Hospital). There were 52 (30.6%) orphans and 68 (40%) children had lost one parent. There were 116 (68.2%) children attending school. Of the 48 (28.2%) who were not, 35 (72%) were too sick and 10 (20.8%) could not afford the fees. Only 59% of those who were older than 8 years knew their HIV serostatus.

There were 139 (81.2%) children taking Triomune, a generic fixed-drug combination of lamivudine, stavudine and nevirapine (Cipla Ltd, India). Sixteen (9.4%) were taking Duovir N, a combination of nevirapine, zidovudine and lamivudine. Ten (5.9%) were taking Combivir or Duovir, a fixed-drug combination of zidovudine and lamivudine, together with efavirenz. Only five (3%) were taking other combinations.

TABLE 1. *Children's socio-demographic characteristics.*

Characteristics		Frequency (%), n=170
Gender	Female	97 (57.1)
	Male	73 (42.9)
Age* (yrs)	2–4.9	18 (10.6)
	5–9.9	64 (37.6)
	10–14.9	63 (37.1)
	15–18	25 (14.7)
Distance from hospital	⩽10 km	110 (64.7)
	>10 km	60 (35.3)
Orphans	Not orphans	50 (29.4)
	Lost both parents	52 (30.6)
	Lost one parent	68 (40.0)
School	Attending school	116 (68.2)
	Not attending school	54 (31.7)
Disclosure to child	Disclosed	71 (41.8)
	Not disclosed	48 (28.2)
	N/A†	51 (30.0)
Duration of HAART (mths)	1–6	78 (45.9)
	7–12	62 (36.5)
	13–24	22 (12.9)
	⩾25	8 (4.7)

* Mean age 9.8, median 10; † not applicable to children <8 years.

One hundred and forty (82.4%) of the children had been on HAART for 1 year and eight (4.7%) had been on ART for >24 months.

In 57 (33.5%) families, the father was the primary caregiver who provided financial support. Of all the primary caregivers, 33 (19%) were mothers, 41 (24.1%) were aunts, 24 (14.1%) were grandmothers and 7 (4.1%) were older siblings. Sixty (35.3%) caregivers were self-employed. Twenty-nine (17.1%) earned more than the equivalent of $125/month, 91 (53.5%) earned the equivalent of $5–80/month and 25 (14.7%) earned <$5/month. Thirty-six caregivers (21.2%) had received tertiary education, 42% secondary education and 36.4% had had only primary or no formal education.

Adherence levels were different for each measure (Table 2).

Using home-based unannounced pill counts as the standard, the positive predictive value, negative predictive value, sensitivity and specificity were calculated (Table 3). There was an intermediate degree of agreement between self-report and clinic-based pill counts (κ 0.44). However, there was no correlation between home-based unannounced pill counts and the other two, κ 0.11 for home-based

TABLE 2. *Adherence levels using different measures.*

Adherence measure	⩾95% adherence % (n)	Mean % adherence (95% confidence interval)	Median (range)
Clinic-based pill counts (n=170)	94.1 (160)	98.54 (97.0–100.0)	100 (0–100)
3-day self-report (n=170)	89 (152)	97.39 (95.4–99.3)	100 (0–100)
Home-based unannounced pill counts (n=164)	72 (118)	94.2 (92.1–96.3)	100 (7–100)

TABLE 3. *Validity and reliability of tests using home-based pill counts as a standard.*

	Self-reported (%)	Clinic-based pill counts (%)
Positive predictive value	50	33.3
Negative predictive value	73	74.5
Sensitivity	18	7.1
Specificity	93	95

unannounced pill counts and self-reported and κ 0.03 for home-based unannounced pill counts and clinic-based pill counts.

Factors affecting adherence

Using home-based unannounced pill counts, the children who had been hospitalised twice or more before starting HAART were more likely to have ⩾95% adherence than those who had been hospitalised once or not at all ($p=0.03$, OR 0.436, 95% CI 0.20–0.92). On the other hand, children whose caregiver was the only one who knew the child's serostatus were three times more likely not to adhere to HAART ($p=0.02$, OR 3.34, 95% CI 1.14–9.82). The other child characteristics were not significantly associated with adherence to HAART (Table 4).

TABLE 4. *Child factors that affect adherence to HAART using unannounced pill counts.*

Variable		Non-adherence $n=46$ (%)	Adherence $n=118$ (%)	OR (95% CI)	p-value
Gender	Female	25 (26.3)	70 (73.7)	1.22 (0.61–2.43)	0.56
	Male	21 (30.4)	48 (69.6)		
Age	0–11 yrs	29 (27.3)	75 (72.1)	0.98 (0.48–1.96)	0.95
	⩾12 yrs	17 (28.3)	43 (71.7)		
>10 km from hospital	Yes	16 (30.8)	36 (69.2)	0.82 (0.40–1.69)	0.59
	No	30 (26.8)	82 (73.2)		
Total orphans	Yes	13 (26.5)	36 (73.5)	0.89 (0.42–1.90)	0.77
	No	33 (28.7)	82 (71.3)		
Attending school*	Yes	30 (26.3)	84 (73.7)	0.76 (0.35–1.63)	0.48
	No	14 (31.8)	30 (68.2)		
Disclosed to*	Yes	18 (27.3)	48 (72.7)	0.91 (0.39–2.07)	0.82
	No	14 (29.2)	34 (70.8)		
Symptomatic	Yes	23 (32.4)	48 (67.6)	1.45 (0.73–2.89)	0.27
	No	23 (24.7)	70 (75.3)		
WHO stage	3	14 (28.0)	36 (72.0)	1.00 (0.47–2.10)	0.99
	1 and 2	32 (28.1)	82 (71.9)		
Hospitalisations before ART	⩾2	29 (23.6)	94 (76.4)	0.44 (0.20–0.92)	0.03†
	<2	17 (41.5)	24 (58.5)		
HIV+ siblings	Yes	7 (20.0)	28 (80.0)	0.57 (0.23–1.43)	0.23
	No	39 (30.2)	90 (69.8)		
Social support*	Yes	10 (26.3)	28 (73.7)	0.89 (0.30–2.66)	0.83
	No	8 (28.6)	20 (71.4)		
No interference with daily life	Yes	39 (28.9)	96 (71.1)	1.27 (0.50–3.23)	0.60
	No	7 (24.1)	22 (75.9)		
No-one else knows child's serostatus	Yes	8 (53.3)	7 (46.7)	3.34 (1.14–9.82)	0.02†
	No	38 (25.5)	111 (74.5)		

* Eligible children only; † significant, $p<0.05$; OR, odds ratio; CI, confidence interval; ⩾95% adherence is adherence, <95% adherence is non-adherence.

None of the caregiver or drug characteristics was significantly associated with adherence using home-based unannounced pill counts.

Logistic regression was undertaken to identify variables independently associated with ⩾95% adherence to HAART. Of the twelve variables with p-values <0.02, only two remained significantly associated with ⩾95% adherence to HAART (Table 5).

Discussion

On average, the study children on HAART took 94.2–98.5% of their medication. Different adherence measures might complement each other and it is therefore recommended that more than one measure be used to increase their sensitivity.[16] Our findings obtained different levels of adherence using the three measures. Using home-based unannounced pill counts, only 118 (72%) of the 164 children had ⩾95% adherence. There was no correlation with the other measures used, similar to other studies using multiple measures.[17–19]

However, other studies in adults have shown close correlation between all three measures. In Uganda, Oyugi and colleagues found that multiple measures used in adults were highly correlated in a paying adult population.[20] Giordano *et al.* also found close correlation between various adherence measures in adults.[21]

Average adherence using home-based unannounced pill counts was much higher than that reported by Bangsberg *et al.* who suggested that average adherence in most studies using objective measures is about 70%.[22] Similarly in Giordano's study, mean adherence by unannounced pill counts (UPC) was 75% in adults.[21] However, using UPC, the mean adherence level of 94% was similar to Oyugi's study in a research institute in Uganda with a range of 87–91% adherence using different measures which had good correlation in adults.[20]

Our self-report findings are similar to another self-report study in children in which 16% missed more than 5% of their medication (84% reported >95% adherence).[23]

Our adherence level was higher than in many other self-report studies in children. For instance, Reddington *et al.* found that 17% of children had missed doses in the previous 24 hours (83% were adherent compared with 92.4% in our study) and 43% reported missing at least one dose in the previous week.[13] In Gibb's study, full adherence the previous week was found in 74% of children[24] and Van Dyke found full adherence in 79% of children,[25] both by self-report. Findings in the present study were also higher than in Byakika's study in three centres in Kampala in which about 72% reported ⩾95% adherence in a population of adults paying for their drugs.[26]

Possible explanations for the greater adherence in our study might be as follows. Firstly, about 82.4% of the children had been on HAART for ⩽1 year and were probably not yet tired of taking the medicine. Secondly, 91% of the children were taking medication with a simple twice-daily dosing schedule, i.e. Triomune and Duovir N. Thirdly, only 21% reported side-effects. Fourthly, children and caregivers are given three adherence counselling sessions before starting ART, and adherence is emphasised by all staff in the clinic. In addition, the

TABLE 5. *Predictors of adherence by logistic regression.*

Variable	Adjusted OR (95% CI)	p-value
⩾2 hospitalisations before HAART	2.42 (1.09–5.37)	0.029*
No-one else aware of child's serostatus	0.29 (0.09–0.90)	0.033*

* Significant, $p<0.05$.

majority of the children were receiving free therapy; only two children in the study were paying for ARVs at that time. However, our results could be an over-estimate as we excluded young children (taking drugs by suspension) and those who forgot pill boxes.

Adherence might have been exaggerated by self-reporting because studies have shown that, compared with electronic monitoring, it consistently over-estimates adherence by 20–25%.[27] Adherence is exaggerated to please the provider or because of recall bias.[28] Since ARVs were free in this study, the caregivers might have perceived researchers as providers and over-reported adherence to please them. Despite its limitations, self-reporting has been found to correspond to viral load.[25,29–32] A meta-analysis of 65 studies to determine characteristics that would correspond to viral load found that not ascertaining confidentiality of responses, an adherence threshold $<95\%$ and a higher percentage of patients on their initial antiretroviral regimen were among characteristics associated with higher estimates.[33] Since these were all present in this study, self-reported adherence might have been over-estimated.

Furthermore, self-reporting had low sensitivity but very high specificity, 37% and 95%, respectively, when surprise home visits for pill counts were used as a gold standard.[28] This was similar to our study in which sensitivity and specificity were 18% and 93%, respectively. It is therefore not a good screening test.

Self-reporting usually records greater adherence than pill counts. In our study, however, pill counts recorded greater adherence than self-reporting. Some caregivers admitted removing the extra pills because they were expected to return empty pill boxes.

Two or more hospitalisations prior to starting HAART was associated with better adherence. The reason for this is not clear because no adherence counselling is given for children admitted to hospital. It might be that caregivers are more motivated and determined to avoid further admission. The children whose caregivers had not disclosed the child's serostatus to anyone had worse adherence. This is probably because they feared stigmatisation. This implies that if that caregiver is not available, the patient is more likely to miss doses because others do not know the value of the medicine and the consequences of missing doses. Similar findings were made by Reddington *et al.* in whose study non-adherent caregivers were more concerned about the child's friends and teachers discovering that the child had HIV infection.[13] Disclosure did not affect adherence, in agreement with Gibb's study.[24] The age of the children did not affect adherence, unlike previous studies in which adherence was poorer in adolescents.[21,32]

None of the factors associated with drugs affected adherence. Only two children recruited were buying their own medication, so we could not assess the effects of cost on adherence. The price of ARVs is a major hindrance to adherence.[26,34] The ARV regimen has been reported to affect adherence in children.[25] In a study by LeProvost *et al.*, adherence to once-daily abacavir/lamivudine was good with only eight of 118 (7%) completed questionnaires reporting non-adherence in the previous 3 days. Acceptability of once-daily drugs was best when the whole regimen was given once daily.[15] In our study, 155 (91.2%) children were taking a similar, twice-daily dose of Triomune and Duovir N. Although adherence was worse in those who had been on HAART for more than 24 months, the difference was not statistically significant.

The study was limited by the fact that we did not ascertain that the prescribed drugs were actually dispensed before the subjects went home. Normally, the dispenser puts four pills in each of the fourteen sections of the pill box. All extra pills found in the pill boxes were considered to be missed doses. However, this error was minimised by asking for an explanation for the extra pills and these were all recorded to ensure that the extra pills were actually missed pills.

In conclusion, about three-quarters of the children had ⩾95% adherence using unannounced pill counts. When only the primary caregiver was aware of the child's HIV serostatus, the children were three times more likely not to adhere to HAART. Two or more hospitalisations before HAART was associated with better adherence. Parents or caregivers should be encouraged to disclose the child's status to at least one other person before starting HAART. With the rapidly growing number of children in the clinic on HAART, other strategies such as home visits, peer counselling and community support groups need to be incorporated into the care programme.

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