EVALUATION OF A PRACTICAL METHOD TO ASSESS ANTIRETROVIRAL ADHERENCE IN HIV-INFECTED THAI CHILDREN

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Abstract. The objective of this study was to evaluate a practical method to assess adherence to antiretroviral therapy by observing virological and immunological responses. We conducted a 12-month longitudinal cohort study of 162 HIV-infected Thai children. Adherence was assessed using 5 methods (self reporting calendar, records of missed doses, pill counts, physician assessment, and an interview questionnaire). CD_4 count, percentage and viral load were performed at baseline and at 12 months. Mean adherence rates at 2, 6, and 12 months were 98, 100, and 99% by the calendar method; 98, 100, and 100% by recording missed doses; 96, 96, and 92% by pill count; and 90, 94, and 97% by physician assessment. Poor agreement (kappa $\leq$ 0.1) was found among the methods. There was a statistically significant difference ($p = 0.05$) in virological response between participants with $\geq$ 95% adherence (0.8 $\log_{10}$) and those with < 95% adherence (0.2 $\log_{10}$) when pill counts were used to assess adherence. In conclusion, despite poor agreement among these tools, a pill count appeared to be the only practical, validated method to differentiate the virological outcome between those who were fully and partially adhere to the treatment regimen.

INTRODUCTION

The Thai Ministry of Public Health (MOPH) launched a National Access Program for Antiretrovirals for people living with HIV/AIDS (NAPHA) in the year 2000. Along with providing antiretroviral (ARV) drugs, the program provides coverage for basic laboratory tests, including complete blood count, SGPT and CD_4 counts and percentages every 6 months (MOPH, 2004). However, an inevitable challenge of this program has been to assess and strengthen ARV adherence.

The primary objective of this study was to evaluate ARV adherence by using five different adherence assessing methods. The secondary objectives were to determine the association between ARV adherence and clinical outcomes and to evaluate the accuracy of these adherence assessment methods. The goal was to find a practical and validated method to assess ARV adherence and to promote the use of this method as a part of long term follow-up care of HIV-infected Thai children in the NAPHA program. The hypothesis for validated tools is that they should agree with one another and the adherence assessed by this tool should be associated with treatment response, validated by CD_4 improvement and viral load suppression.

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MATERIALS AND METHODS

Study design

We carried out a 12-month prospective study at the Siriraj Hospital Pediatric Clinic. Of approximately 220 HIV-infected children who were followed at this clinic, 169 children who required ARV therapy received ARV through the NAPHA program. Study recruitment started simultaneously with the 2003 NAPHA program in March 2003 and ended in March 2004. Inclusion criteria were HIV-infected children who were taking ARV or were naïve and required ARV. Institutionalized children and children who were severely symptomatic were excluded. Follow-up was scheduled every two months. The study was approved by the institutional review board of Siriraj Hospital. Written informed consent was obtained from each child's caregiver.

Adherence assessment tools

Adherence was assessed using four different practical and easy to implement tools, which were a self reporting calendar, a self reporting record of missed doses, pill counts and physician assessment by visual analog scale at 2 months, 6 months and 12 months following the enrollment. Assessment at 2 months was used as baseline because some children were ARV naïve at the time of enrollment. A questionnaire was included as an additional tool at the 12-month visit.

Self reporting calendar and record of missed doses

Both the self reporting calendar and the record of missed doses were take-home tools. Each patient was randomly placed into the "calendar group" or the "record of missed doses" group. The patients received and returned the tools at each clinic visit.

Interviewed questionnaire

The questionnaire used in this study was a Thai translated version of the Pediatric AIDS Clinical Trial Group (PACTG) adherence questionnaire, modules I and II. This translated version combined the two modules into one form. In the first module, the number of missed doses in the past three days was asked. Adherence was then calculated as the number of doses taken divided by the number of doses that should have been taken. In the second module, reasons for poor adherence were identified. Interviewed questionnaires were completed at the twelfth month visit by a child psychologist who was not involved in medication dispensing and was not aware of the child's clinical response. The psychologist was not involved in medication dispensing and was not aware of the child's clinical response.

Pill counts

All ARVs were dispensed at the clinic by pharmacists. To receive their medications, subjects needed to return their leftover medications from their last visit. The average adherence percentage for each ARV was used to represent their overall adherence at each visit.

Physician assessment

At each clinic visit, one of six Pediatric Infectious Disease physicians who evaluated the subject would assess the adherence level using a visual analog scale. He/she would make an "x" mark on this 100 mm scale. Given that 100 mm equals 100% adherence, the distance of the "x" mark from the beginning of the scale was calculated as the adherence percentage.

Immunological and virological data

CD_4 counts were assessed at baseline, 6 months and 12 months. Immunological failure was defined as either a decrease of more than 30% in the CD_4 absolute count from baseline or a decrease of more than 5% in the CD_4 percentage from baseline for children whose baseline CD_4 was <15% (MOPH, 2004). HIV PCR was measured by the Roche Amplicor-transcribed PCR method at baseline and 12 months. The lower limit of detection

was 400 copies/ml. Virological success was defined as either an undetectable HIV RNA level at 12 months or a decrease by more than ten fold ($1.0\log_{10}$) from baseline.

Statistical analysis

Adherence assessed by each tool, for each participant, at each clinic visit, was calculated as a percentage. Full adherence was defined as an adherence level more than or equal to 95%, while partial adherence was defined as less than 95%. Kappa statistics were used to assess the agreement among each pair of tools. The chi-square test was used to test the association between categorical variables, which were adherence levels and CD_4 counts and percentages as well as a log of the viral load. The Fisher's exact test was also used where appropriate. Changes in the log for HIV RNA and CD_4 counts and percentages between full and partial adherence were compared using the Mann-Whitney U test. A two tailed p-value of <0.05 was considered statistically significant. Statistical analyses were carried out using SPSS system version 11.5 (Chicago, IL).

RESULTS

One hundred sixty-two children were enrolled. Participant clinical characteristics are described in Table 1. Different ARV adherence assessing tools yielded different estimates of adherence levels.

For all self reporting tools, (*ie* calendar, record of missed doses and questionnaires), adherence levels were consistently high with a mean adherence level greater than 95%. Mean adherence rates at 2, 6 and 12 months were 98% (n=48), 100% (55), and 99% (52) by calendar; 98% (n=36), 100% (32), and 100% (28) by record of missed doses; 96% (n=112), 96% (135), and 92% (125) by pill counts; and 90% (n=93), 94% (143), and 97% (132) by physician assessment. A trend of higher mean adherence levels with each sub-

sequent visit was noted.

One hundred thirty-seven (85%) caregivers completed their questionnaires. Almost 70% reported no missed doses in the 3 days prior to the interview. Reasons commonly attributed to poor adherence were forgetfulness, bad taste and interruption of the child's rest. Reasons for not completing the questionnaires were due to missed appointments

Table 1
Clinical characteristics.

Characteristics	No. (%)
Age (years)	
Preschool, < 7	104 (64)
School age, 7-10	36 (22)
Early teenagers, 11-14	22 (14)
Sex	
Female	78 (48)
Male	84 (52)
Baseline CD4 percentage	
< 15 %	65 (40)
15-25 %	64 (40)
>25 %	33 (20)
Baseline viral load (copies/ml)	
<10,000	47 (29)
10,000-100,000	37 (23)
>100,000	43 (27)
N/A	35 (21)
Antiretroviral (ARV) history	
ARV naïve	62 (38)
ARV experienced	100 (62)
Current ARV regimen	
Dual NRTI	46 (28)
NNRTI containing regimen	104 (65)
PI containing regimen	12 (7)
Clinical CDC classification	
N	15 (9)
A	45 (28)
B	68 (42)
C	34 (21)
Persons who administered medications	
Self	13 (9)
Biological parents	72 (50)
Relatives	59 (36)
Missing data	18 (11)

Table 2

Treatment outcomes and ARV adherence at 6 and 12 months: immunological changes and adherence; virological changes and adherence.

Table 2a. Immunological changes and adherence.

| Adherence assessing tool | Adherence percentage | CD4 increase at 6 months | | | | | CD4 increase at 12 months | | | | |
| | | CD4% gain from baseline | | | % of absolute count increase from baseline | | CD4% gain from baseline | | | % of absolute count increase from baseline | |
		n	Median	Mean	Median	Mean	n	Median	Mean	Median	Mean
CAL	< 95%	3	7.4	4.8	52.8	53.3	2	9.7	9.7	135.5	135.5
	≥ 95%	52	3.4	4.4	18.7	244.3	50	4.5	6.6	7.2	496.9
REC	< 95%	1	2.1	2.1	31.4	31.4	1	1.92	1.92	31.3	31.3
	≥ 95%	31	5.3	4.6	24.8	660.9	27	3.92	5.88	5.6	1,019.4
PC	< 95%	22	6	5.5	7.7	128.1	20	3.8	4.8	4.1	74
	≥ 95%	113	3	3.9	16.9	328.3	105	3.4	5.5	11.6	552
PA	< 95%	69	2.5	4.2	16.9	212.1	66	4.6	6.2	14.2	387.4
	≥ 95%	74	3.9	4.0	9.7	319.5	66	1.7	4.6	-2	506.9
QUES	< 95%	1	4	4	-7	-7	1	-2.4	-2.4	-15.5	-15.5
	≥ 95%	133	3.9	4.3	16.9	286.2	123	4.3	5.8	9.7	482.6

Table 2b. Virological changes and adherence.

| Adherence assessing tools | Adherence level | n | Log viral load change at 12 month from baseline | |
			Median	Mean
CAL	< 95%	2	-1.2	-1.2
	≥ 95%	36	-0.2	-0.5
REC	< 95%	1	0.08	0.08
	≥ 95%	20	-0.3	-0.99
PC[a]	< 95%	17	0	-0.2
	≥ 95%	76	-0.2	-0.8
PA	< 95%	45	-0.2	-0.7
	≥ 95%	54	-0.02	-0.6
QUES	< 95%	1	-2.26	-2.26
	≥ 95%	90	-0.1	-0.6

[a] p= 0.05 for the statistical association between log of viral load change and adherence at 12 month visit (those with ≥ 95% adherence at 12 months had significantly lower logs of viral loads than baseline compared to those with < 95% adherence)

CAL = self reporting calendar, REC = self reporting record of missed doses, PC = pill count, PA = physician assessment, Ques = interviewed self reporting questionnaires.

and caregiver refusals.

This study showed consistently poor agreement (kappa ≤ 0.1) between each pair of adherence assessment tools.

By the end of the twelfth month, 111 children had viral load measured and 147 had a CD_4 count performed at baseline and at 12 months. One hundred thirty-eight of 147 children (98.9%) did not have immunological failure. Fifty-five of 111 (49.5%) children had virological success.

Table 2a shows that participants whose adherence was ≥95% assessed by any method had a higher percentage of absolute CD_4 count compared to those whose adherence was < 95%. For example, when adherence was assessed by pill count at 12 months, those who had ≥95% adherence had a mean percentage increase in the absolute CD_4 count of 552% and a mean 5.8% gain in CD_4% while those who had < 95% adherence had 74% mean increase in absolute CD_4 count and mean 4.8% gain in CD_4%. The number of participants who had adherence level of <95% was relatively small when adherence was assessed by self-report methods (calendar, records of missed doses and questionnaires). This is likely due to the tendency of these methods to over report adherence levels when compared to pill counts and physician assessment.

In Table 2b, when using pill counts as the assessment method, participants with ≥ 95% adherence had a mean viral load decrease of 0.8 fold (0.8 $\log_{10}$), which was a statistically significant difference from those with < 95% adherence with a mean viral load decrease of 0.2 fold (0.2 $\log_{10}$) (p=0.05). The association between virological response and adherence level assessed by self report methods was limited by the small number of children reporting <95% adherence.

Among those who completed the laboratory work-up, 30 children were ARV naïve and 77 were ARV experienced. There was no statistically significant difference in immunological responses and adherence levels between medication naïve and experienced children. However, children who were ARV naïve had a higher rate of virological success (67.6%) than children who were ARV experienced (41.6%).

DISCUSSION

Although antiretroviral adherence is crucial for ARV treatment outcome, determining adherence continues to be a difficult and challenging task. Self reporting adherence is frequently used, but its reliability as well as its tendency to overestimate has been a concern (Liu *et al*, 2001). As in this study, self reporting tools reported much higher adherence levels than other tools. Similar to the underestimated trend seen in other studies, physician assessment reported the lowest adherence levels (Paterson *et al*, 2000; Gross *et al*, 2002). Pill counts, however, appear to be the most objective and practical method to measure adherence. Obstacles for pill counts may occur, such as pill dumping or forgetting to return medications (McNabb *et al*, 2001).

A relatively high adherence level among HIV-infected Thai children was reported in this study when compared to other pediatric literature (Watson and Farley, 1999; Reddington *et al*, 2000; Van Dyke *et al*, 2002; Farley *et al*, 2003; Gibb *et al*, 2003). In this study, the mean adherence levels were consistently more than 90% with any tools used. An adherence study in 72 HIV-infected children using pharmacy records for the first 180 days of HAART, found that only 58% of children maintained an adherence greater than 75% (Watson and Farley, 1999). A study using questionnaires administered by caregivers yielded full adherence (forgotten no doses in the last 7 days) in 78% of 266 returned questionnaires (Gibb *et al*, 2003). In a study using Medication Event Monitoring

System (MEMS) in HIV-infected children, the adherence rate was reported from 13 to 98% (Farley *et al*, 2003).

Many studies have documented an association between adherence levels and virological response (Haubrich *et al*, 1999; McNabb *et al*, 2001). A meta-analysis of 65 studies containing 15,351 subjects showed that studies using an adherence threshold lower than 95% yielded higher odd ratios of adherence-virological response relationship than studies using a threshold higher than 95% (Nieuwkerk *et al*, 2005). Our study, using a 95% cutoff, yielded a significant association between adherence assessed by pill counts and virological response. We postulated that the consistently high reported adherence levels when self reporting tools were used did not allow differentiation between those that truly had partial adherence and full adherence. Therefore, association could not be determined.

It is well established that with increasing antiretroviral experience, the likelihood of virological response decreases (Paterson *et al*, 2000; Nieuwkerk and Oort, 2005). This study showed that antiretroviral ARV naïve children had better virological responses than experienced children.

One study was limited by the nature of self-reporting tools, which tended to overestimate favorable results. Social desirability has also been an obstacle for adherence assessment. This is especially true in regard to self-reporting methods in Thailand, where cultural factors differ from those found in other developed countries, where most adherence studies were conducted.

In summary, the use of different adherence assessment methods led to different measured results. Multiple methods may be needed to assess adherence and its trends over time. Importantly, repeated adherence assessment serves as adherence assistance in itself. Despite poor agreement between adherence assessment methods in this study, pill counts proved to be the most useful and the only method that was statistically associated with virological response.

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