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Discordance Between Providers Estimated and Caregivers Self Reported Adherence to HAART and Immunological Response Among HIV Infected Children in Ethiopia

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Abstract

Purpose*:* Poor concordance between patient and physician reports of adherence might lead to inappropriate decisions regarding therapy. This study was undertaken to determine the rate of discordance between caregivers of children and physicians on adherence to Highly Active Antiretroviral Therapy (HAART).

Methods: In a cross sectional study involving 390 respondents that was conducted in five hospitals in Addis Ababa, agreement between caregiver-reported adherence and providers' estimate of adherence was compared using Kappa (k) statistic. The association between the CD4 counts and measure of adherence was evaluated using a receiver operating characteristic (ROC) curve.

Results: Caregivers reported dose adherence was 87% in the last 7 days and physician estimated 84% of the children as adherent based on their judgment. Fair agreement was observed between caregivers-reported dose adherence and providers' estimate adherence (Kappa = 0.27, p=0.0001). In a ROC curve, the association between a current CD4 count slope and physician estimated was poor.

Conclusions: There is fair agreement and high rate of discordance (18%) between physicians estimated and caregivers reported adherence. These recall for an intervention to augment better mutual understanding between physicians and caregivers on the issue of adherence to HAART under clinical care programme.

Keywords: Adherence; CD4 count; Discordance; HAART.

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Introduction

An estimated 370,000 [330,000 – 410,000] children under 15 became infected with HIV in 2007 [1]. The course and outcome of human immunodeficiency virus (HIV) disease have been substantially changed by the introduction of highly active antiretroviral therapy (HAART), which has been effective in reducing the need for hospital admissions and antibiotic courses, and leading to a significant improvement in the quality of life [2,3].

Near perfect adherence to ART therapy is critical for clinical and virologic success in HIV-infected patients. It is widely believed that clinicians tend to overestimate medication adherence. However, there are adherences in adult patients, showing that clinicians fail to identify non-adherent patients (false negatives) but when they believe a patient is not adherent (true-positives) they are generally correct [4, 5, 6]. In the clinical management of HIV, decisions to start or to change therapy, and type of therapeutic regimen, may be decided by screening patients for adherence [7]. Several methods to assess adherence, such as patient self-report, electronic monitoring systems, and pill count have shown acceptable validity and feasibility [8, 9, 10].

In clinical practice, adherence assessments are frequent having suggested that physicians are poor at judgng whether or not patients are taking their medications [8, 11]. Poor concordance between patient and physician reports of adherence might lead to inappropriate decisions regarding therapy. Measuring adherence to treatment of pediatric HIV is a major challenge for researchers and clinicians [12]. Several Studies have shown that available adherence measures have limitations, raising questions about how best to measure drug-taking behavior [13]. WHO has recommended use of CD4 cell count measurements and clinical outcomes for monitoring ART in the absence of Viral Load [14]. We evaluated the association between adherence measurement and their effect on immunological response in HIV infected children. The aim of this study was to assess the level of discordance on adherence rates to HAART as reported by caregivers of children with those obtained in the same time by interviewing the physicians in charge of the children.

Methods

Study design and procedures

The study was carried out in selected antiretroviral therapy units in five Addis Ababa Hospitals including Black Lion, St Peter, Yekatit 12, Zewditu, and ALERT Hospitals. Administratively, each of the hospitals is divided into sub-city to serve patients from each of the ten sub-cities. The hospitals are the only hospitals providing HIV treatment to children at the time of data collection. According to the report obtained from the registration record at the time of the study, 1,624 children were registered for ART in the hospitals that received HAART and on follow-up in the ART unit. respectively. This facility-based cross-sectional study was conducted from February 18 - April 28, 2008. A total of 390 HIV infected children with their caregivers were enrolled in the study from registered ART cases in the selected hospitals.

The sample size was calculated using two proportions sample size formula with Epi Info (WHO, Geneva/CDC, Atlanta, USA, 2005) 6.04 statistical package. The following parameters were used to calculate the sample size: proportion of adherence (P1) among male children, 33%; proportion of adherence (P2) among female children, 20% [15]; 95% CI and 80% power. This gave a sample size of 393. Adding 10% for non-response rate, the total sample size was 433. A simple random sampling technique was employed to identify the study units using the ART unique numbers from the registration book in each hospital.

Further description on the methodological procedures has been described in detail elsewhere [16]. Children who fulfilled the following criteria were included in the study: receiving continuous antiretroviral therapy for the last 12 weeks before study in the selected hospital and the caregivers were parents or guardians that were counseled on the importance of drug adherence and how to recognize common adverse drug reactions associated with antiretroviral drugs. Children who were terminally ill or aged from 3 months to 14 h and caregivers in a moribund state were excluded.

The management of HIV/AIDS in Ethiopia is based on the National Guideline for Implementation of the Antiretroviral Therapy Programme in Ethiopia developed by the Federal HIV/AIDS Prevention and Control (HAPCO) under the Ministry of Health (MOH). Institutional Ethical Review Committee of Jimma University and Research Ethics Committee of Addis Ababa Health Bureau approved the study protocol. Caregivers gave verbal informed consent for participating in the study.

Measurements

The dependent variable for this study was discordance of estimation by caregivers - reported and providers estimated adherence. Data were collected using a structured questionnaire (in English), which was adopted from previous studies. The content of the questionnaire included: socio-demographic characteristics (age of the child, sex of the child, age of the caregivers, ethnicity, educational status, occupational status of the caregivers); socio-economics conditions (monthly income, financial support for the child, grant for the child); medication related factors; Health care delivery systems related factors including access to care, disclosure status of the children; perception related to the services, diagnosis, referral and treatment, medication administration including adherence measurement.

The questionnaire was translated to Amharic and retranslated back to English by different person to check for its consistency. The data was collected in prospectively from those who came for treatment in a clinical visit in their respective hospitals. The data was collected by five trained nurse councilors who worked closely with the caregivers as well as children. A total of three days intensive training was given for all supervisors and data collectors.

Medical charts were reviewed to collect clinical and immunological markers (CD4 count) of children. The CD4 counts used where those from actual laboratory findings at baseline before initiating ART and after 6 months thereafter.

Statistical analysis

Data entry and analyses was carried out using SPSS version 12.0.1 statistical packages. One trained data clerk entered and cleaned the data. Univariate statistics for each adherence measure and bivariate associations between the adherence measures were calculated. We evaluated each antiretroviral adherence measure with baseline and current CD4 count. Providers' estimates of adherence predictions of immunological response were evaluated as the area under the receiver-operating characteristic (ROC) curve. The two adherence measures were compared on the basis of previous day, same day of study, 3 and 7 days later caregivers self reported (number of doses reported missed) and the providers estimated adherence on Ministry of Health (MOH) formatted sheet along with other medical record. Agreement between self-reported adherence and providers' estimate of adherence was compared using kappa (k) statistic.

The association between adherence measures and Immunological response was estimated by Pearson and Spearman's correlation values, with a $p < 0.05$ considered statistically significant. Criterion validity was established through the calculation of

sensitivity, specificity, ROC (ceceiver operator characteristic) curve area and positive and negative predictive values.

In this study a child was said to be adherent if he/she took more than 95% (no missing of one dose of all prescribed doses of ART therapy in the last 7 days) or non-adherent if he/she took less than 95% (missing at least one dose of all prescribed doses of ART therapy in the last 7 days). Adherence was classified as good if providers' estimate of adherence is ≥95%. If a patient has missed ≤ 3 doses in a month the treatment was considered fair. However, if a patient had missed 3-8 doses in a month, the adherence was considered to be poor. Discordance in this study implies that the estimated caregiver reported adherence to ART and the physician estimated adherence differ in any case.

Results

Sociodemographic characteristics of respondents

The socio-demographic characteristics of the respondents are reported in Table 1. From 390 respondents, majority of the children (205, 52.6%) were above 9 years. Majority (297, 76.2%) of the caregivers were orthodox by religion and either had no job or mainly engaged in poorly paid jobs. Most of them (176, 45.1%) had only primary school education. One hundred thirty four (34.4%) and 56 (14.4%) of the children lived with their biological mothers and grandmothers, respectively. Majority of the caregivers (277, 71%) that no financial support. Fathers and local NGOs provided support to some of the children. About 277 (71.4%) of the respondents had household income level below <=500 Eth.Birr per month.

Clinical characteristics of respondents

Most of the children 193(49.5%) were in stage III based Of WHO classification. The mean and median CD4 count were 273.28 cells/mm^3 and 203.00 cells/mm^3 before ART, and 576.92 cells/mm^3 and 497.50 cells/mm^3 at the time of the study. One hundred ninety-four (49.7%) of the children had CD4 count of <200 cells/mm3 at the start of the treatment. Similar number of children had CD4 count of >=500 cells/mm3 at the time of the study.

Table 1: Demographic and social characteristics of caregivers and children in Addis Ababa, Ethiopia [N=390], April 2008

Variable	Frequency (%)
Age	
<3 years	15 (3.8)
3-5 years	43 (11)
6-8 years	127 (32.6)
≥9 years	205 (52.6)
Sex of the child	
Boy	175 (44.9)
Girl	215 (55.1)
Ethnic group of the caregivers	
Amhara	207 (53.1)
Oromo	94 (24.1)
Tigere	35 (9)
Gurage	52 (13.3)
Others *	2 (0.5)
Religion of the caregivers	
Orthodox	297 (76.2)
Catholic	21 (5.4)
Protestant	45 (11.5)
Muslim	18 (4.6)
Others #	9 (2.3)
Occupational status of the caregivers	
Farmer	4 (1)
Merchant	55 (14.1)
Governmental employee	58 (15.9)
NGO	29 (7.4)
Day laborer	103 (26.4)
Jobless/ house made	80 (20.5)
Marital status of the caregivers	
Single	38 (9.7)
Married	174 (44.6)
Divorced	40 (10.3)
Widowed	138 (35.4)
Educational status of the caregivers	
Unable to read and write	94 (24.1)
Primary (1-8)	176 (45.1)
Secondary (9-12)	68 (17.4)
Diploma and above	52 (13.3)
Family income [a]	
<=105	277 (71)
106-150	50 (12.8)
151-262	61 (15.6)
>263	2 (0.5)

Others *-Harari, Somali
Others #-- Mission, Jehovah
[a] Exchange rate 1 USD = 8.6 Ethiopian Birr (ETB)

Table 2: Medicals markers of HIV infected children in Addis Ababa, Ethiopia, [N=390] based on caregivers self reporting, April 2008

Variable	Frequency (%)	
	Adherent	non-adherent
WHO Clinical stage of HIV disease		
Stage I	14(4.13)	1(2)
Stage II	102(30.1)	9(17.6)
Stage III	163(48.07)	30(58.8)
Stage IV	60(17.7)	11(21.6)
CD4 counts at start of treatment		
<200	164(48.4)	30(58.8)
200-499	131(38.64)	16(31.4)
>=500	49(12.96)	5(9.8)
Current CD4 count		
<200	45(13.3)	12(23.5)
200-499	119(35.1)	20(39.2)
>=500	175(51.6)	19(37.3)
Provider's estimate of adherence		
Good	295(87)	33(64.7)
Fair	36(10.64)	11(21.6)
Poor	8(2.36)	7(13.7)

Almost all 328(84.1%) of the physician estimated good adherence rate for the child (Table 2).

Medication administrations and caregivers reported adherence

A total of 51 children (13.1%) omitted at least one dose of antiretroviral drugs in the past 7 days before the survey. Caregivers self reported dose adherence was 87% in the last 7 days and physician estimated 84% of the children as adherent based on their judgment (Figure 1).

When the reliability of the two estimates for adherence to ART was evaluated in a dichotomous analysis defining adherence ≥95% of the dose taken, both the caregivers interviews and physician judgment were significant (p=0.001). But there was discrepancy between clinicians' estimate of dose adherence and caregivers self reported adherence. Fair agreement was observed between caregivers self-reported dose adherence and providers' estimate adherence with (Kappa = 0.27, p=0.0001). In 298 of 390 cases (76.4%), patients and physicians agreed on adherence, and in 22 cases (5.64%) they agreed on nonadherence. In 29 cases (7.74%) patients reported nonadherence and were judged adherent by the physician, while in 41 cases (10.5%) self-reported adherent patients were estimated to be nonadherent. Thus, a total of 70 physician-patient pairs (18%) were discordant (Table 3). Using patient-assessed adherence as reference, the study revealed that the physician estimated adherence had the sensitivity, specificity, positive predictive value, and negative predictive value of 0.87 (0.83-0.90), 0.372 (0.24-0.50), 0.902 (0.87-0.93), and 0.301 (0.19-0.41), respectively.

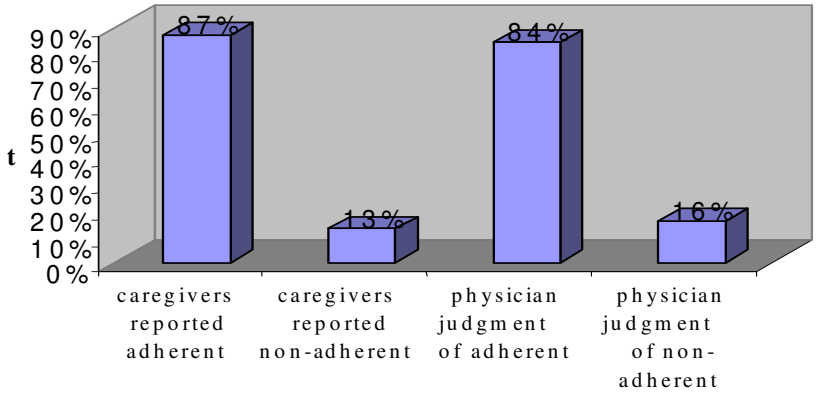

Figure 1: Adherence to ART in HIV infected children according to caregivers' interviews and physician judgment in Addis Ababa, Ethiopia, April 2008

The test efficiency was 80.5 % (Table 4).

For further estimation and accuracy of the physician judgment, we use a ROC curve. The ROC statistics revealed that the curve lies little above the reference line. Hence, the estimation by physician is somewhat inaccurate for adherence. The area under the curve for the ROC curve was 0.57 (95%CI=0.48-0.65) indicating a low performance of the estimation of adherence (Figure 2).

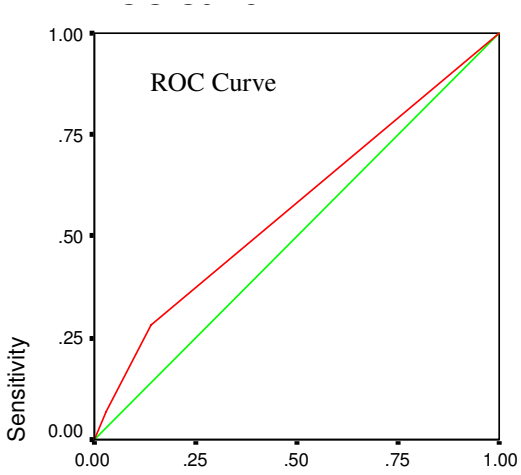

Figure 2: Receiver operating characteristic (ROC) curve assessing the association between caregivers self reported physician estimated adherence (area under the curve = 0.57)

Associations among measures of adherence and immunological marker

The correlation between caregivers reported adherence and physician estimated adherence was marginally correlated with (n = 390, r = -0.222 and p = -0.222, P <0.01).

Table 3: Comparison of the diagnostic value of self reported adherence as compared to physician estimated adherence in Addis Ababa, Ethiopia, April 2008

		Self Reported Adherence Estimation		
		Adherent #(%)	Non adherent #(%)	Total #(%)
Physician Estimated Adherence	Adherent	298(91.1)	29(8.87)	327(100)
	Non adherent	41(65)	22(35)	63(100)
	Total	339(86.9)	51(13.1)	390(100)

Table 4: Measures of validity percent and ROC curve area of Physician-estimated adherence in relation to the reference point/self reported adherence in Addis Ababa, Ethiopia, April 2008

Measures of Validity	Physician-Estimated Adherence (95%CI)
Sensitivity	87(0.83-0.90)
Specificity	37.2(0.24-0.50)
Positive Predictive value	90.2(0.87-0.93)
Negative Predictive values	30.1(0.19-0.41)
Test Efficiency	80.5
Measure of agreement between the two tests (Kappa)	Kappa = 0.27, P=0.0001
ROC curve area	57 (0.48-0.65)

Table 5: Description and summary statistics of adherence measures plus correlations among adherence measures with baseline and current CD4 count in Addis Ababa, Ethiopia, April 2008

		Correlation Pearson's (r), Spearman's rho (n)			
Adherence Measure and Units	Measurement method	caregivers repotted adherence	physician estimated adherence	Baseline CD4 count	Current CD4
Caregivers reported	Percent of total regimen medication taken by caregivers self report	1	-0.222** -0.222** (n=390)	0.066 0.069 (n=390)	0.115* 0.112* (n=390)
Physician estimated	Percent of total estimated by physician	-0.222** -0.222** (n=390)	1	-0.106* -0.104* (n=390)	-0.146** -0.140** (n=390)

** Correlation is significant at the .01 level (2-tailed); * Correlation is significant at the .05 level (2-tailed)

The measure significantly associated with the baseline CD4 count was physician estimated adherence (r =-0.106, p = -0.104, n = 390, p<0.05) while caregivers reported adherence estimation (r =0.115, p = 0.112, n = 390, p<0.05) and physician estimated adherence (r =-0.146, p = -0.140, n = 390, p<0.01) were significantly associated with the current CD4 counts. The pair wise correlations between caregivers self reported adherence and baseline CD4 counts were not significant (p>0.05) (Table 5).

Discussion

Different methods have been used to measure adherence. However, there has not been any consensus on the measurement method that can be taken as the gold standard [17]. The current study intended to assess the two measurement of adherence and their immunological response among HIV infected children in resource-limited settings.

The observed rate of discordance was 18 % which showed a total of 70 physician-patient pairs. In an earlier study, the rate of discordance on adherence to drugs between patients and physicians was 35% [18] which is significantly lower than what we have reported. Again, the rate of discordance in our study is lower than that previously reported in HIV-infected people where adherence was measured by electronic monitoring 41% [8], self-report 45% [11] or even with a study carried out on adherence to treatment for diabetic adolescents [19]. Despite the fact that the rate of discordance is lower than in some other studies, substantial gap has been found between patients and physicians. In this study, the physicians were more often discordant with patients when they rated the children as non-adherent as the caregivers rated them as adherent. Poor concordance between patients and physicians is likely to lead to physician misclassification of patient's adherence that can lead to potentially unnecessary or harmful changes in drug therapy, including withholding or withdrawal of medications.

Non-adherent patients judged as adherent by their physicians may receive drugs they do not take or that are not useful for their therapy. In the current study, the sensitivity and positive predictive value of the physician estimation for children adherence was high in relation to the reference. But in contrary to this, the prediction of physicians estimation was less specific to adherence judgment. In similar context with an earlier study, it was found that the sensitivity of clinical judgment for detecting nonadherence was 10% [20]. In a previous study on HIV-infected people,

physicians miscategorized adherence for 41% of people [8] and in a study on intravenous drug users, 60% of people self-reporting nonadherence was classified as adherent by their physician [21]. In one study using pill count, they reported the sensitivity and specificity of provider estimates of non-adherence were 40% and 85%, respectively, with sensitivity and specificity of patient interview being 72% and 95%, respectively [22]. In our study, caregivers reported adherence was found to be overestimated as compared to physician judgment. Similar finding has been found in patient self-report adherence elsewhere [23, 24]. The higher rate of caregiver adherence that was pronounced might be because of improved adherence just before the health care visit or over reporting of adherence by participants because of social desirability. Self reported adherence has shown an index of utility in different resource rich and poor setting. For this reason, self-reported had been used as a common adherence measure [25, 26]. These findings are consistent with those of another recent study that validated both self-reported adherence and measures of protease inhibitor concentrations as predictors of virologic response [27, 28].

Although self-reporting has been found to overestimate adherence in comparison with adherence measurements made by MEMS, in a study by Bangsberg *et al.* [29], structured patient reporting of adherence is strongly associated with adherence measured by unannounced pill counts and MEMS. Even, an electronic monitoring system was found to be a less sensitive predictor of virologic response than self-reported adherence [30]. These and other finding suggests that it is reasonable to use patient self-reporting to monitor adherence routinely in the clinical setting.

Unlike in our study where physicians estimated adherence were correlated with the baseline CD4 count, Haubrich *et al*. did not find any correlation between physician's estimated adherence to antiretroviral correlated and the patient self-assessment of adherence nor with virologic or immunologic outcomes [11]. But we must take into account that physician estimated adherence has low specificity in our context. The need for additional studies to predict adherence in local setup is of the essence.

The main limitation of this study was recall bias; there is no gold standard assessment of adherence; caregivers might be prone to social desirability bias. Despite the above limitation, the study had several strength including use of more than one method of adherence assessment, inclusion of several sites, evaluation of adherence measurement with CD4 count, and the inclusion of respondents from diverse socio-demographic background.

Conclusion

There is discordance between caregivers-reported dose adherence and providers' estimate adherence in this study. The physician adherence estimation has low specificity and negative predictive value but high sensitivity and positive predictive values. Further studies are needed to understand the factors that can facilitate the concordance between patient and physician estimation of adherence that can able to improve the children treatment outcomes.

Authors' contributions

SB conceived and designed study, performed analysis and interpretation of data and drafted the manuscript, AD assisted with the design, interpretation of data and the critical review of the manuscript, AA assisted with the conception and design the study and critically reviewed the manuscript, KD conceived and designed the study, critical reviewed the manuscript. AB participated in design and helped to draft the manuscript. All authors approved and read the final manuscript. All authors participated in critical appraisal and revision of the manuscript.

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