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Adherence to Antiretroviral Therapy in HIV-Positive Adolescents in Uganda Assessed by Multiple Methods

A Prospective Cohort Study

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Abstract

Background: The effectiveness of traditional adherence measurements used in adolescent populations is difficult to assess. Antiretroviral (ARV) adherence research among adolescents living with HIV in resource-constrained countries is particularly challenging and little evidence is available.

Objectives: The primary objective of this study was to determine the feasibility of a large-scale, long-term study using electronic adherence monitoring in Uganda. The secondary objective was to compare accuracy of pill count (PC) and self-report (SR) adherence with electronic medication vials (eCAPs™).

Methods: Adolescents receiving ARV therapy at the Joint Clinical Research Centre in Kampala, Uganda, were recruited. ARVs were dispensed in eCAPs™ for 1 year. Person-pill-days (PPDs) [1 day where adherence was measured for one medication in one patient] were calculated and a weighted paired t-test was used to compare the levels of adherence among subjects for three different adherence measurement methods.

Results: Fifteen patients were included: 40% were female, mean age was 14 years, mean baseline CD4+ cell count was 244 cells/μL, and average treatment duration was 9 months at study entry. Overall, 4721 PPDs were observed. Some eCAPs™ required replacement during the study resulting in some data loss. Consent rate was high (94%) but was slow due to age limit cut-points.

Overall adherence for SR was 99%, PC was 97% and eCAP™ was 88% ($p < 0.05$ for all comparisons). 93%, 67% and 23% of patients had an adherence of greater than 95% as measured by SR, PC and eCAP™ methods, respectively.

Conclusions: A large-scale adherence study in Uganda would be feasible using a more robust electronic monitoring system. Adherence measurements produced by PCs and self-reporting methods appear to overestimate adherence measured electronically.

Background

Adherence to antiretroviral (ARV) medications is among the most important factors to ensure immunologic, viral and clinical response in the treatment of HIV.[1] Among the various treatment groups, adolescents are often labeled as high risk with respect to adherence. Although several large adult cohorts in Africa have been studied with respect to medication adherence, there is a relative paucity of prospective cohort studies involving children and adolescents.[2-4] A recent study from southern Africa showed that adolescents had lower adherence, decreased viral suppression and immunologic recovery along with a higher rate of virologic rebound after initial suppression than in adults.[5] These results contrast with a recent Ugandan

study involving HIV-positive children, adolescents, and adults, which found no statistically significant differences in outcomes (however a clinically significant difference could not be ruled out).[6]

The best method to monitor adherence remains controversial. While methods such as pill counts (PC), patient adherence disclosure (self-report [SR]), and refill monitoring are commonly used, several studies have suggested that these methods produce falsely elevated adherence rates.[7,8] A more costly method of medication adherence monitoring has been the use of electronic medication vials, such as eCAPs™, or medication event monitoring systems (MEMS™). These devices effectively time-stamp each vial opening, thus eliminating the need for patient recall or PCs to determine adherence rates. The differences found between electronic methods of adherence measurement and 'traditional' methods such as PCs and SR may be of significant importance. It is highly possible that adherence thresholds for optimal viral suppression may require re-investigation using a more reliable method of measurement.

Very little research has been conducted describing adherence patterns in adolescent, HIV-positive cohorts. The majority of studies conducted in children and adolescents, both in Uganda and other resource-poor countries, are cross-sectional in nature and do not provide a good estimation of the natural history of non-adherence.[3,9-11] Given the risk of non-adherence with resultant treatment failure in this population, it is imperative that adherence patterns using both standard methods and electronic methods be studied. Second, with improved knowledge of adherence patterns in this patient population, focused interventions could be implemented that may be both cost effective and, ultimately, life-saving.

This study had a 2-fold objective: (i) to determine the feasibility of conducting a large-scale study of this nature; and (ii) to measure ARV adherence using both traditional methods (PC and SR) and to compare these methods with electronic adherence measurement using the eCAP™ system.

Methods

Population and Intervention

The Joint Clinical Research Centre (JCRC) is a multisite treatment center with locations throughout Uganda that, among other activities, provides clinical care to children and adolescents living with HIV. Adolescent children aged between 12 and 17 years were recruited at the JCRC site in Kampala (Mengo campus), Uganda, between May 2008 and April 2009 for enrollment into this study. Exclusion criteria included having received ARV therapy for more than 1 year, pregnancy, lack of a permanent address and life expectancy of less than 1 year as determined by the attending physician. This study was approved by the JCRC institutional review board, the Ugandan National Council of Science and Technology, and the clinical research ethics board at BC Children's Hospital, Vancouver, BC, Canada.

For enrolled patients, ARV medications were dispensed in eCAP™ vials. At the time of medication refills, adherence data was downloaded into an electronic database. PC data as well as patient SRs of non-adherence were also collected on refill days by research assistants. Patients were followed until their eCAP™ vial became non-functional. If the vial became non-functional prior to 1 year of follow-up the vial was replaced. The study continued until the supply of vials was exhausted.

Outcomes

The outcomes for feasibility included recruitment and consent rates as well as all aspects of electronic vial use, including eCAP™ durability, patient comfort with eCAP™ use (elicited subjectively by investigators training children in vial use) and ease of analysis. The primary clinical outcome was measurement of the proportion of patients with perfect adherence (>95%), good adherence (90–94.9%), poor adherence (80–89.9%) and very poor adherence (<80%) according to the three adherence measures (eCAP™, PC, and SR). Adherence was measured for each dosing interval according to each adherence method. For the eCAPs™, all missed doses were identified by non-opening events. Missed doses were subtracted from the total required doses. Self-reported adherence was determined through a questionnaire administered at the time of each refill. Each subject was asked how many doses they had missed during the previous prescription period and this number was subtracted from the required doses. PCs were also conducted at the time the questionnaire was administered. All pills were counted by research assistants and the remaining pills were subtracted from the number of doses required during that particular period (if patients came early for refills this was accounted for during PCs, as were late refills).

Statistical Analysis

Feasibility endpoints were described using simple descriptive statistics. For the clinical endpoints, all person-pill-days (PPDs) were calculated for each subject. One PPD was equal to 1 day where adherence was measured for one medication in one person. Because of missing data, the within subject overlap

between adherence measurement methods was not complete; therefore, each subject had total PPDs calculated for eCAP™, SR, and PC separately. For each refill period (generally 28 days) the number of adherent days (partial days were allowed since some medications were dosed twice daily) was determined for each measurement method and the period adherence was determined for each period, in each subject, by each method. The proportion of patients in the pre-defined adherence categories was calculated (overall adherence for the total study period). Differences in adherence as measured by the three different adherence measures were calculated using paired t-tests, not accounting for multiple comparisons since these were exploratory analyses. Comparisons were made only between overlapping periods (i.e. if one period did not have eCAP™ data due to eCAP™ malfunction this period was excluded for comparative analyses). All analyses were weighted according to total duration of overlapping follow-up in each subject.

Additional period-specific, individual level, longitudinal descriptive analyses were conducted to determine adherence trends. Specifically, exploration of between-medication adherence differences among individual subjects was explored. All analyses were conducted using SAS software (SAS Institute, Cary, NC, USA) and the R Project (http://www.R-project.org). The desired sample size was 25 subjects. No formal sample size estimations based on statistical power were calculated since this was a pilot study.

Results

Sixteen subjects were enrolled in the study. One subject declined participation prior to receiving medications and was excluded from the final analysis. Overall, 40% of participants were female, the mean age was 14 years (range 12–17 years), mean baseline CD4+ cell count was 244 cells/μL, and the average treatment duration was 9 months at the time of study entry (table I). While the consent rate was high (94%), the rate of recruitment was slow secondary to the relatively narrow age limit cut-points. Nearly 1 year was required to enroll 15 patients. Over the course of the study several vials ceased functioning prematurely. This resulted in data loss (approximately 15%) for several patients and limited enrollment to 15 patients rather than the desired sample size of 25 patients. Reasons for malfunction were not determined. In all cases of premature malfunction, vials were replaced at the subsequent refill. Subject training for vial use was straightforward and no significant barriers were identified with respect to vial use by the youth recruited.

Table I. Baseline characteristics of subjects

Characteristic	n = 15
Age [y; mean (range)]	14 (12–17)
Sex [no. of females (%)]	6 (40)
CD4+ cell count [cells/μL; mean (±SD)]	244 (166)
Months since diagnosis [mean (±SD)]	27 (20)
Months since treatment initiation [mean (±SD)]	9 (6)

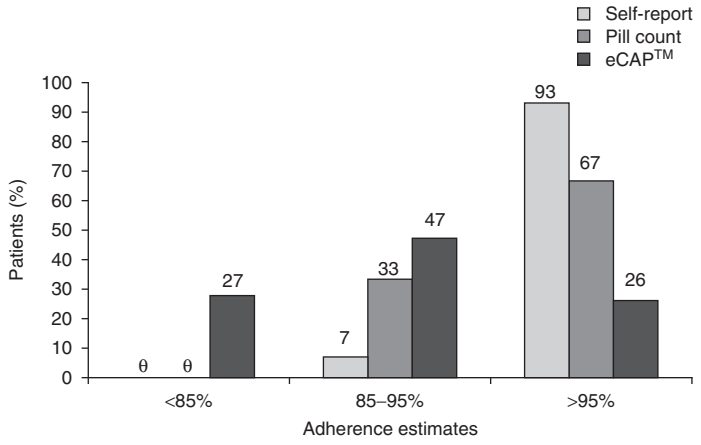

Fig. 1. Adherence threshold by measurement type. This figure shows the distribution of three different methods of adherence measurement according to three pre-defined thresholds of adherence. θ = zero; **eCAP**™ = electronic medication vial.

Over the course of the study a total of 4721 PPDs were generated among 15 patients. A longitudinal examination of the eCAP™ data showed that while most non-adherence among individual subjects was time-dependent (during times of poor adherence all medications were affected), some was drug-dependent (adherent to one medication but not others). The limited pilot sample precluded a regression analysis to further explore this effect. Overall, the adherence for SR was 99%, PC was 97% and eCAP™ was 88%. Figure 1 shows the distribution of adherence estimates among the three methods of measurement for pre-defined adherence cut-offs. In most individuals, SR and PC estimated significantly higher adherence rates compared with electronic monitoring (figure 2). The weighted adherence differences between eCAP™ and SR was 12.1% (95% CI 6.7, 17.6) [figure 2a], between eCAP™ and PC was 10.4% (95% CI 4.3, 16.5) [figure 2b], and between SR and PC was 1.7% (95% CI 0.3, 3.1) [figure 2c].

Discussion

This study showed that a large longitudinal adherence study aiming to better quantify adherence patterns among HIV-positive adolescents is feasible, although multiple sites would

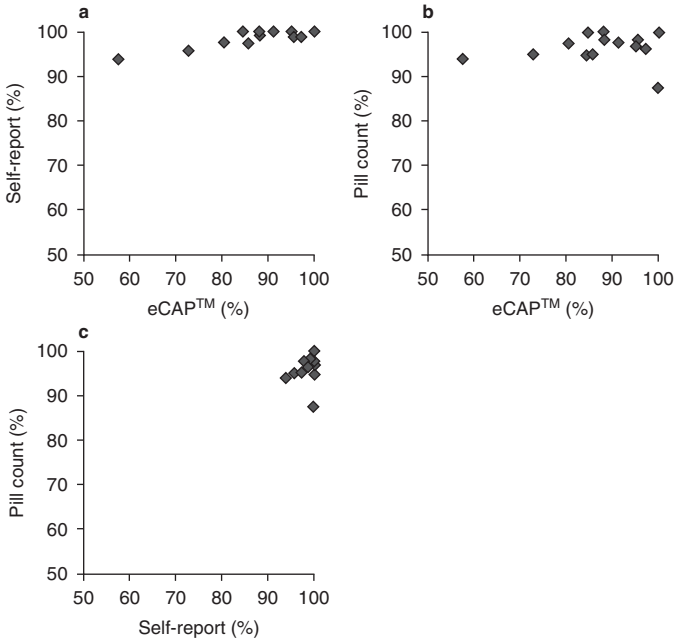

Fig. 2. Between-method adherence rates by patient: (**a**) self-report vs eCAP™; (**b**) pill count vs eCAP™; (**c**) pill count vs self-report. Perfect concordance between methods would result in subject markers being aligned along a 45 degree axis between the two comparative methods. **eCAP**™ = electronic medication vial.

probably be required for a major study. This study also showed that adherence measurements produced by PCs and self-reporting methods produce a significantly higher estimate of adherence than electronic adherence measurement methods using eCAPs™. It appears likely that the true adherence is more closely determined using electronic methods and that future research using adherence as the outcome of interest should use electronic methods as the gold standard. A recent systematic review of adherence interventions found that out of 26 studies conducted only one used electronic monitoring for adherence assessment.[12] It is probable that the effect size of any adherence promoting intervention would be more accurately measured using electronic means than an alternate objective (i.e. PCs) or subjective (i.e. SRs) method.

These results are important since they represent the longest adherence study among adolescents in a resource-poor setting using electronic adherence measures, and one of only a handful that monitor adherence for more than several weeks. It is important that future studies use electronic adherence measurement as a gold standard, especially when exploring the very important issue of adherence-associated viral mutation and subsequent ARV resistance. A recent study published in 2008 found that despite high levels of adherence (determined through PCs) ARV resistance remained a significant problem.[13] These authors concluded that factors other than adherence may be associated with observed resistance. However, it is perhaps more likely that using PCs provided an overestimation of true adherence. Had electronic methods been employed this association might not have been observed. In a recent pediatric study from South Africa, children under 10 years of age were dispensed a single (liquid) ARV medication in MEMs™ caps.[4] Adherence was measured both electronically and by SR using a visual analog scale. This study showed that high levels of adherence with electronic monitoring of just one drug showed high specificity for viral load suppression, whereas SR did not. Of the few who did have sub-optimal viral suppression despite high adherence as measured my MEMs™, poor adherence to other agents may have been the cause. Data from the present study showed that this is possible since adherence to one agent was not always associated with adherence to others.

This report is not without limitations. First, the small sample size limits external validity and thus the ability to generalize results to the adolescent population living in resource-poor areas. However, it was not our intention to develop a protocol with strong generalizability even if we had attained our target sample size of 25 patients. Our primary focus was internal validity, and since subjects were used as their own control for all comparisons the internal validity is strong, justifying conclusions made among methods of adherence measurement. Despite the small sample this study had adequate power to demonstrate significant differences between eCAP™ measurements and SR/PC. An inherent limitation to all adherence research using electronic vials is the unproven assumption that when a vial is opened a pill is taken. In fact this may not have been the case. In this study, the primary calculation of non-adherence was made only when there was no opening for a specific dosing time. This is the most reliable and conservative measure of adherence. It is recognized, however, that one opening may have resulted in more than one pill being removed, thus resulting in an under-estimation of true adherence. While this study attempted to measure adherence using several methods, it did not seek to explain reasons for poor adherence. It could be hypothesized that normal adolescent behaviors such as peer pressure, rebellion, and possible HIV-related sigma may have played a significant role among those with poor adherence. A further limitation of electronic-based adherence research is higher cost compared with traditional methods of adherence measurement (each vial cost $Can45.00 in 2007). While the use of electronic vials is unlikely to be a feasible strategy to monitor adherence for clinical purposes, we believe that the expense for research is justified given the aforementioned limitations of the traditional methods of SR and

PCs. Finally, the repercussions of malfunctioning vials was not trivial and led to 40% reduction in anticipated sample size as well as an approximate 15% loss of data. Future research must ensure the robustness of their electronic data collection tool to prevent similar data loss.

Conclusions

Electronic adherence measurement methods are likely to produce more reliable measures of adherence in adolescents in resource-poor areas. Further larger studies are required to determine the effect of long-term adherence, as measured using electronic means, on treatment failures and progression of HIV in adolescent populations.

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