Published in final edited form as:

AIDS Behav. 2015 April ; 19(4): 626–634. doi:10.1007/s10461-015-0998-x.

Comprehensive Evaluation of Caregiver-Reported Antiretroviral Therapy Adherence for HIV-Infected Children

Rachel C. Vreeman[1,2,3], **Winstone M. Nyandiko**[2,4], **Hai Liu**[5], **Wanzhu Tu**[5], **Michael L. Scanlon**[1,2], **James E Slaven**[5], **Samuel O. Ayaya**[2,4], and **Thomas S. Inui**[2,3,6]

[1]Children's Health Services Research, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States

[2]Academic Model Providing Access to Healthcare (AMPATH), Eldoret, Kenya

[3]Regenstrief Institute, Inc., Indianapolis, IN, United States

[4]Department of Child Health and Paediatrics, Moi University School of Medicine, Eldoret, Kenya

[5]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, IN

[6]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

Abstract

For HIV-infected children, adherence to antiretroviral therapy (ART) is often assessed by caregiver-report but there are few data on their validity. We conducted prospective evaluations with 191 children ages 0 to 14 years and their caregivers over 6 months in western Kenya to identify questionnaire items that best predicted adherence to ART. Medication Event Monitoring Systems® (MEMS, MWV/AARDEX Ltd, Switzerland) electronic dose monitors were used as external criterion for adherence. We employed a novel variable selection tool using the LASSO technique with logistic regression to identify items best correlated with dichotomized MEMS adherence (≥90% or <90% doses taken). Nine of 48 adherence items were identified as the best predictors of adherence, including missed or late doses in the past 7 days, problems giving the child medicines, and caregiver-level factors like not being present at medication taking. These items could be included in adherence assessment tools for pediatric patients.

Keywords

Pediatric HIV care; Adherence; Best Practice; Resource-Limited Setting

CORRESPONDING AUTHOR: Dr. Rachel Vreeman, Children's Health Services Research, Department of Pediatrics, Indiana University School of Medicine, 410 W. 10th Street, HITS Suite 1000, Indianapolis, IN, 46202. rvreeman@iu.edu. Telephone: 317-278-0552. Fax: 317-278-0456.

DISCLAIMER: The views expressed in this article are those of the authors and do not necessarily represent the view of the Indiana University School of Medicine or the Moi University School of Medicine. The authors have no conflicts of interest to disclose. The primary author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

INTRODUCTION

An estimated 3.4 million children under 15 years of age are infected with the Human Immunodeficiency Virus (HIV), with upwards of 90% living in sub-Saharan Africa [1]. Antiretroviral therapy (ART) significantly reduces HIV-related morbidity and mortality [2–6] but good clinical outcomes require high and consistent adherence to ART [7–11]. Currently, no gold standard exists for how to accurately measure adherence to ART in routine clinical care, especially for HIV-infected children in resource-limited settings [12].

Adherence to ART is most commonly assessed through self-reported missed doses [13] and in the case of young HIV-infected children through caregiver report [14, 15]. Data are conflicting on the reliability of caregiver report to measure children's adherence to ART [16, 17]. Validated caregiver reported measures from the NIAID Pediatric Clinical Trials Group Studies have shown good correlation with virologic outcomes among children in the United States [18] but these measures have not been rigorously evaluated in resource-limited settings. Studies from sub-Saharan Africa that have investigated caregiver-reported adherence questions related to recall of missed doses in a certain period of time have indicated higher levels of adherence compared to more "objective" assessment methods like pill counts, pharmacy refill, and electronic drug monitoring (EDM) [19–21]. EDM is often the best measure in terms of correlation with virologic outcomes [22, 23], but is not recommended for routine adherence monitoring [24] and is too expensive for widespread use in resource-limited settings [25].

Routine assessment of adherence to ART is recommended by the International Association of Physicians in AIDS Care for all patients [24] and is essential to guide clinical decision-making, especially in resource-limited settings where second- and third-line regimens are not typically available [26]. The objective of this study was to identify questionnaire items that could be asked to caregivers to accurately assess ART adherence among children in a large HIV treatment program in western Kenya. In this manuscript, we describe the first stage of the development of a reliable and valid pediatric ART adherence questionnaire.

METHODS

Study design

We conducted a prospective study utilizing a rigorous, iterative process to evaluate questionnaire items designed to measure pediatric adherence to ART and associated factors among 200 caregivers of HIV-infected children receiving care through the Academic Model Providing Access to Healthcare (AMPATH) in Eldoret, Kenya. Item selection for the adherence questionnaire was informed by literature review, expert panel consultation, and formal qualitative work in this setting in western Kenya [27, 28]. Qualitative methods included individual and group cognitive assessments with caregivers of HIV-infected children about adherence items using verbal probing and guided "thinking aloud" to evaluate relevance, comprehension, recall, sensitivity, and acceptability of the questions. Key findings from qualitative analysis included differences in responses by recall period, benefits of including normalizing statements before asking for sensitive information,

challenges processing categorical frequency scales, and optimized response items and question wording [28].

Together, these efforts yielded 48 items for assessing adherence to ART among Kenyan children that were compiled into a questionnaire. Questionnaire items included late doses and missed doses (in the past 3, 7 and 30 days), doses taken by visual analog scale (VAS), adherence barriers, social barriers like HIV/AIDS stigma, and household characteristics (questionnaire included in Electronic Supplementary Materials). The items were translated into Kiswahili, one of the regional and national languages, with good face validity and understandability [28]. We only present data from questionnaire items administered to the caregivers; child participants who reported responsibility for their medication taking were asked questions about their adherence but these will be reported elsewhere.

Children were followed for exactly 6 months and each caregiver had the adherence questionnaire administered to them a total of 7 times at approximately 1 month intervals. Trained study personnel verbally administered the adherence questionnaire in Kiswahili or English (dependent on caregiver's preference) to caregivers at study visits. Adherence items were evaluated by comparison with Medication Event Monitoring Systems® (MEMS, MWV/AARDEX Ltd, Switzerland) that use a microcircuit to record the time and date whenever the medication bottle is opened. At study initiation, all study participants received and were trained in using the MEMS bottles and data from MEMS were downloaded at monthly study visits. MEMS were chosen as the reference measure as they show better correlation with virological outcomes compared to other adherence measures like pharmacy refill or pill counts and have been used in similar studies evaluating adherence measures [23]. MEMS also allow for investigating patterns of adherence, which may be particularly important for the design of adherence interventions. This study was approved by the Institutional Review Board at Indiana University School of Medicine in Indianapolis, Indiana, USA and by the Institutional Research and Ethics Committee at Moi University School of Medicine in Eldoret, Kenya.

Study participants

The study population was dyads of caregivers and their HIV-infected children ages 0 to 14 years. The children were on either a nevirapine- (NVP) or efavirenz- (EFV) based first-line ART regimen and enrolled in care at AMPATH – a large HIV treatment program in western Kenya [29, 30]. Caregiver-child dyads were followed for 6 months of prospective adherence assessments. HIV infection was defined as having one positive HIV DNA PCR test or one positive HIV ELISA antibody test. Children above 14 years of age were not enrolled as they are usually treated in the AMPATH adult care setting. As the primary objective of this study was to evaluate caregiver-reported adherence, we focused on younger children as older children take more responsibility for their own medication taking and likely have very different adherence challenges as they enter early- to mid-adolescence. Caregivers were defined as an individual who accompanied the child to clinical and study visits and reported having responsibility or knowledge of the child's medication taking. Caregivers could be primary or secondary, biological or non-biological caregivers. Clinic nurses and clinicians, as well as study staff, screened a convenience sample of clinic attendees for potential study

participants who met inclusion criteria and referred them to learn about the study. Participants could also self-refer. Out of a total of 210 caregivers and children approached to participate in the study, 10 declined to participate. Informed consent was obtained for all caregivers and assent for any child 10 years and above following standard locally-approved research protocols. A small incentive was provided for participation to help cover transportation costs and time.

Data analysis

We used a novel variable selection method called the Least Absolute Shrinkage and Selection Operator (LASSO) to select adherence questionnaire items that best correlated with dichotomized MEMS adherence [31, 32]. Unlike traditional multivariate regression models that suffer from numerical instability when examining a large number of independent variables, the LASSO-based variable selection method helps to shrink the less important regression coefficients to zero, leaving only the items that strongly correlate with the adherence outcome in the model. In this study, we used the variable selection method to identify items that were most predictive of MEMS adherence. MEMS adherence was dichotomized as ≥90% or <90% of all doses taken at each monthly study visit. Dichotomization at the level of 90% was chosen to be consistent with other studies comparing adherence measures to MEMS [33, 34]. Moreover, studies show that adherence below 90% significantly increases the risk for virologic rebound and drug resistance [35–37].

LASSO models were run for each study visit except baseline (total of 6 variable selection models). We used visit-level variable selection logistic regression models as the primary analysis to detect factors that correlated with concurrently measured ART adherence because adherence exhibits temporal variations [38]. Items that showed consistency in their correlation to MEMS adherence across LASSO models (defined as significant at 2 or more study visits) were used to calculate a summary risk score for non-adherence. The risk score was intended to test whether a composite measure of multiple items correlating well with MEMS adherence could be used together to predict patients at risk of non-adherence. The risk score was calculated as the sum of individual items weighted by the corresponding regression coefficients. We then assessed the accuracy of the summary score of the selected items in predicting the dichotomized MEMS adherence outcome at each visit. We examined the receiver operating characteristic (ROC) curves of the risk score and reported the area under the ROC curve (C-statistic) for each visit. To increase the robustness of analysis, sensitivity analyses were conducted at different MEMS adherence dichotomization points (80%, 85%, 95%, and 99%) and no significant differences were found in the items selected by LASSO or by the items' predictive value. Thus, only the results from dichotomizing adherence at the 90% level are presented.

In addition to visit-level analyses, we conducted repeated measures logistic regression analysis to assess the association between LASSO-selected independent variables (i.e., variables significant in LASSO analysis at 2 or more study visits) and dichotomized MES adherence (≥90% or <90%) over time. Sensitivity analyses using different adherence dichotomization points were also performed, as described above. We used the generalized

estimating equation (GEE) technique to accommodate within-subject correlation from repeated measures. In the multivariate model, patients' baseline demographic variables were adjusted as covariates (age, gender, and duration on ART) and we ran correlation matrices on adherence items selected by the LASSO method to ensure proper model fit. Adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) are reported. Statistical analyses were performed using R 3.0.1 (Vienna, Austria) and SAS v9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Study Participant Characteristics

One hundred ninety-one caregiver-child dyads completed the study (9 out of the original 200 participants did not complete the study because they withdrew from the study or the child died). Mean age of HIV-infected children at enrollment was 8.2 years and 55% were female (Table I). Children had a mean weight-for-age Z (WAZ) score of −1.7, which is low but within the "normal" range (WHO classifies a WAZ score between −2 and 2 as within the "normal" range, <−2 as mild malnutrition, and <−3 as severe malnutrition) [39]. Most children were on twice daily NVP-based regimens (77%) versus once-daily EFV-based regimens and mean duration on ART was 2.3 years. Only 23% of caregivers reported that their child knew their HIV status. Most caregiver participants were the child's biological mother (63%) but a number of biological fathers (11%) and grandparents (7%) participated as well. When caregivers were asked to list all persons who had partial or full responsibility for the child's medication taking, biological mothers were most commonly responsible (84%), followed by the child's sibling (42%), father (36%), or other relative in the home (36%). Thirty-one percent of caregivers reported that the child was at least partially responsible for his or her own medication taking. Poverty was high in this cohort; 70% of caregivers reported there was not enough food for their family in the past 30 days and 83% reported having financial difficulty with transportation to clinic.

Median adherence was 93% by MEMS over the 6-month period but improved over the course of the study (Figure I). While 51% of children had ≥90% MEMS adherence at month 1, 64% achieved ≥90% MEMS at month 2, and between 67–68% at following months. Only 29% maintained ≥90% MEMS adherence over the course of 6 months. MEMS treatment interruptions were common in this cohort; 49.5% of children had at least one treatment interruption of ≥48 hours in 6 months with a median of 3 treatment interruptions per child during the study period (range 0 to 17, IQR 0–6). There were few missing adherence data; over 94% of children had complete MEMS adherence data across all visits, while 4% of children had missing data at only 1 visit and 2% of children had missing data at 2 visits. No children had missing adherence data at 3 or more visits.

Adherence item selection

Eighteen out of the 48 questionnaire items had non-zero effects in by-visit variable selection regression analyses and thus were correlated with MEMS adherence (Table II). Nine of these items had non-zero effects at 2 or more visits and met the more rigorous criteria for inclusion in the calculation of the risk score and logistic regression analysis. C-statistics

from ROC curve analysis across visits ranged from 0.61 to 0.78. Significant domains of the selected items that were associated with MEMS non-adherence included reported missed doses in the past 7 days and 30 days, doses given more than 1 hour late in the past 7 days, enrollment in AMPATH's nutrition program, difficulty giving the child medicines on time, the child refusing to take the medicines, and a higher number of reported caregiver-level barriers. Caregiver-level barriers were significant at 2 visits (visit 3 and visit 5) and included the caregiver not being around to give the medicines, not wanting to give the medicines around others, and forgetting to give the medicines, among others. Child-level barriers were significant at 3 visits, but showed inconsistent relationships with adherence; at visit 2 and visit 6 reporting child-level barriers was associated with non-adherence but at visit 5 reporting child-level barriers was associated with higher adherence.

After adjusting for demographic characteristics and within-subject correlation, 4 out of the 9 selected items were statistically significant in a repeated measure analysis using GEE (Table III). Items associated with <90% MEMS adherence were problems getting the child to take the medicines (OR 0.43, 95%CI 0.22–0.83), the caregiver reporting 1 or more caregiver-level barriers (OR 2.20, 95%CI 1.06–4.56), missing at least one dose in the past 7 days (OR 1.79, 95%CI 1.07–3.01), and giving a dose more than one hour late in the past 7 days (OR 1.26, 95%CI 1.08–1.47). While it was not significant in the LASSO selection method, a child's duration on ART was associated with MEMS in GEE analysis; longer time on ART was associated with MEMS non-adherence (OR 1.09, 95%CI 1.00–1.19).

DISCUSSION

The results of this study suggest that certain caregiver-report questionnaire items perform better than others in reflecting a child's adherence to ART. While adherence questionnaire items varied widely in their association with MEMS, we identified several items with stronger correlations that may be used as part of low-cost, routine adherence assessment tools for pediatric HIV patients on ART. To our knowledge, this is the first study evaluating caregiver-reported adherence questionnaire items against electronic dose monitoring using this type of variable selection method. Rigorously validated questionnaire items have not previously been available for pediatric adherence evaluation in resource-limited settings, hampering efforts to monitor adherence. Future studies may benefit from this rigorous methodological approach, namely the use of the LASSO section tool, to evaluate the performance of a large and diverse set of questionnaire items related to adherence to ART or in other areas.

A major strength of our study was testing a broad range of adherence items from different domains. Furthermore, the domains informing item inclusion for testing were identified through formative qualitative work in this setting with further cross-cultural adaptation using cognitive interviewing and other qualitative techniques [27, 28]. While commonly used questions about missed doses performed relatively well (at least 30-day and 7-day missed doses), we found that questions around adherence barriers, specifically problems with dose timing, caregiver forgetting, and social issues like HIV/AIDS stigma (adherence barriers included in our questionnaire are given in Table IV), were also predictive of non-adherence among this population. This is consistent with a number of studies that showed more

nuanced caregiver-reported difficulties in giving their child medicines or understanding of medical regimens were associated with viral load [16, 40, 41]. Our findings provide further evidence for the relationship between these broader domains of a family's psychosocial situation and adherence-related behaviors. These results have practical implications for practitioners conducting adherence assessments and counseling with patients and should encourage the further investigation of how psychosocial factors impact adherence and how these barriers can be identified.

For settings like western Kenya, developing low-cost adherence measurement tools is critical. Using the caregiver-reported items that were predictive of MEMS adherence in this study (i.e., 9 items selected by LASSO), we will now undertake further testing and validation of these items in a short-version adherence questionnaire delivered by clinicians rather than research teams. Reliability and validity testing of the short-version adherence questionnaire will be conducted in 3 countries (2 in sub-Saharan Africa and 1 in Asia) using MEMS monitoring again as the reference standard. If successful, it is our hope that this 9-item adherence questionnaire can be used as a global adherence screening tool to identify children who may need further adherence evaluation or adherence counseling and that the tool is brief but reliable enough to use for routine adherence monitoring for all pediatric patients on ART. In busy clinical settings like AMPATH, clinicians do not have time to conduct intensive adherence counseling with children and caregivers; however, a short adherence screening tool using validated items might allow clinic staff to identify children who are at higher risk for non-adherence and can then be targeted for further adherence assessments or interventions. Finally, there is a dearth of data on adherence interventions and counseling for children on ART in resource-limited settings, which is certainly hampered by the lack of reliable adherence measures [42]. A validated adherence questionnaire will allow cheaper and longer follow-up of children to evaluate these interventions and ultimately to improve the care and survival of HIV-infected children.

This study has a number of potential limitations for consideration. First, this study employed convenience sampling that introduces potential selection bias and in this case might have led to children who had excellent adherence or very low adherence being more likely to enroll. Second, our analysis relied on the validity of MEMS to accurately measure adherence. Electronic dose monitoring using MEMS has shown high correlation with viral load levels and has been commonly utilized to both describe adherence and compare adherence measurement techniques in resource-limited settings [17, 19, 25, 43–45]; however, there are a number of potential weaknesses in using MEMS that have not been adequately explored in this setting [44, 46]. We attempted to overcome many of the challenges of daily MEMS use by training and educating the families about how and why to use the MEMS bottles and asking them about any problems or difficulties with the MEMS at each study encounter. Third, participants were aware that their medications were in the MEMS bottles, which may have impacted their medication-taking behavior. We did see a significant increase in adherence to ART by MEMS, particularly from month 1 to month 2, suggesting that some part of the study procedures (e.g., use of MEMS, adherence questionnaire, interaction with study personnel, etc.) may have had an intervention effect. Any such effect on adherence behaviors should not have impacted our results as the goal was to identify which questionnaire items accurately predicted MEMS adherence levels at each visit, whether it

was increasing or decreasing. Fourth, we used visit-level models to evaluate the performance of adherence items. This approach gave us the ability to detect month-to-month changes in associations between independent variables and adherence levels; however, this also weakened our ability to measure overall or composite associations. We addressed this potential weakness by conducting two separate analyses using composite variables across the 6 visits that showed good consistency with the visit-level model (data not shown). Although the variable selection method can effectively identify important independent variables, the estimated non-zero coefficients for the selected items do not have estimation variability measures (i.e., confidence intervals). To overcome this, GEE analysis based on LASSO-selected items was performed to provide the variability estimates. Finally, we used cross-cultural adaptation and grounded formative work to inform the specific wording of questionnaire items and the content of the domains were adapted to the particular cultural context in western Kenya. The suitability of these questions in other settings is unclear though we anticipate that the general domains of inquiry could still be broadly applicable across global pediatric HIV care sites. Further work in reliability and validity testing of the adherence questionnaire items are being undertaken.

CONCLUSIONS

We found that caregiver reported adherence among HIV-infected children varied significantly by different questionnaire items in their association with MEMS. Certain adherence questionnaire items related to missed and late doses and those related to child- and caregiver-level adherence barriers performed better and may be used as part of an adherence screening questionnaire. More extensive validity and reliability testing of these candidate items is ongoing to better inform adherence assessment tools for pediatric adherence to ART in resource-limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would first and foremost like to thank the Kenyan families who took part in this study. We would also like to acknowledge the significant work of key clinicians and nurses at AMPATH in promoting and helping evaluate adherence, including Irene Marete, Edith Apondi, Peter Gisore, Constance Tenge, Esther Nabakwe, John Chumba, Lucy Warui, Mary Rugut, Victor Cheboi, and Christine Mukhwana. This research was supported in part by a grant (1K23MH087225) to Dr. Vreeman from the NIMH and AMPATH Plus with support from the United States Agency for International Development as part of the President's Emergency Plan for AIDS Relief (PEPFAR).

References

1. World Health Organization. Global HIV/AIDS Response: Epidemic update and health sector progress towards Universal Access - Progress Report 2011. Geneva: World Health Organization; 2011.
2. Doerholt K, Duong T, Tookey P, et al. Outcomes for human immunodeficiency virus-1-infected infants in the United kingdom and Republic of Ireland in the era of effective antiretroviral therapy. Pediatr Infect Dis J. 2006; 25(5):420–6. [PubMed: 16645506]

3. Gibb DM, Duong T, Tookey PA, et al. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. BMJ (Clinical research ed). 2003; 327(7422):1019.
4. Gibb DM, Goodall RL, Giacomet V, McGee L, Compagnucci A, Lyall H. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. Pediatr Infect Dis J. 2003; 22(1):56–62. [PubMed: 12544410]
5. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA. 1998; 279(6):450–4. [PubMed: 9466638]
6. Needham DM, Hogg RS, Yip B, O'Shaughnessy M, Schechter MT, Montaner JS. The impact of antiretroviral therapy on AIDS survival observed in a province-wide drug treatment programme. International journal of STD & AIDS. 1998; 9(6):370–2. [PubMed: 9671257]
7. Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. Curr HIV/AIDS Rep. 2007; 4(2):65–72. [PubMed: 17547827]
8. Gavin PJ, Yogev R. The role of protease inhibitor therapy in children with HIV infection. Paediatr Drugs. 2002; 4(9):581–607. [PubMed: 12175273]
9. Mullen J, Leech S, O'Shea S, et al. Antiretroviral drug resistance among HIV-1 infected children failing treatment. Journal of medical virology. 2002; 68(3):299–304. [PubMed: 12226814]
10. San-Andres FJ, Rubio R, Castilla J, et al. Incidence of acquired immunodeficiency syndrome-associated opportunistic diseases and the effect of treatment on a cohort of 1115 patients infected with human immunodeficiency virus, 1989–1997. Clin Infect Dis. 2003; 36(9):1177–85. [PubMed: 12715314]
11. Tam LW, Chui CK, Brumme CJ, et al. The Relationship Between Resistance and Adherence in Drug-Naive Individuals Initiating HAART Is Specific to Individual Drug Classes. J Acquir Immune Defic Syndr. 2008; 49(3):266–271. [PubMed: 18845950]
12. Chesney MA. The elusive gold standard. Future perspectives for HIV adherence assessment and intervention. J Acquir Immune Defic Syndr. 2006; 43 (Suppl 1):S149–55. [PubMed: 17133199]
13. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management. AIDS Behav. 2006; 10(3):227–45. [PubMed: 16783535]
14. Vreeman RC, Nyandiko WM, Blaschke TF. Adherence to antiretroviral therapy for adults and children in resource-limited settings. Reviews in Antiviral Therapy. 2009; 2(Supplement):S6–S13.
15. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. Pediatrics. 2007; 119(6):e1371–83. [PubMed: 17533177]
16. Allison SM, Koenig LJ, Marhefka SL, et al. Assessing medication adherence of perinatally HIV-infected children using caregiver interviews. J Assoc Nurses AIDS Care. 2010; 21(6):478–88. [PubMed: 20452242]
17. Farley J, Hines S, Musk A, Ferrus S, Tepper V. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr. 2003; 33(2):211–8. [PubMed: 12794557]
18. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. Pediatrics. 2002; 109(4):e61. [PubMed: 11927734]
19. Haberer JE, Cook A, Walker AS, et al. Excellent adherence to antiretrovirals in HIV+ Zambian children is compromised by disrupted routine, HIV nondisclosure, and paradoxical income effects. PloS one. 2011; 6(4):e18505. [PubMed: 21533031]
20. Davies MA, Boulle A, Fakir T, Nuttall J, Eley B. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. BMC Pediatr. 2008; 8:34. [PubMed: 18771599]
21. Vreeman RC, Wiehe SE, Pearce EC, Nyandiko WM. A systematic review of pediatric adherence to antiretroviral therapy in low- and middle-income countries. The Pediatric infectious disease journal. 2008; 27(8):686–91. [PubMed: 18574439]

22. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. Clin Infect Dis. 2001; 33(8):1417–23. [PubMed: 11550118]
23. Deschamps AE, De Geest S, Vandamme AM, Bobbaers H, Peetermans WE, Van Wijngaerden E. Diagnostic value of different adherence measures using electronic monitoring and virologic failure as reference standards. AIDS Patient Care STDS. 2008; 22(9):735–43. [PubMed: 18754705]
24. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Annals of internal medicine. 2012; 156(11):817–33. [PubMed: 22393036]
25. Muller AD, Jaspan HB, Myer L, et al. Standard measures are inadequate to monitor pediatric adherence in a resource-limited setting. AIDS Behav. 2011; 15(2):422–31. [PubMed: 20953692]
26. Boyd MA, Cooper DA. Second-line combination antiretroviral therapy in resource-limited settings: facing the challenges through clinical research. AIDS (London, England). 2007; 21 (Suppl 4):S55–63.
27. Vreeman RC, Nyandiko WM, Ayaya SO, Walumbe EG, Marrero DG, Inui TS. Factors sustaining pediatric adherence to antiretroviral therapy in western Kenya. Qual Health Res. 2009; 19(12): 1716–29. [PubMed: 19949221]
28. Vreeman RC, Nyandiko WM, Ayaya SO, Walumbe EG, Inui TS. Cognitive Interviewing for Cross-Cultural Adaptation of Pediatric Antiretroviral Therapy Adherence Measurement Items. Int J Behav Med. 2014; 21:186–196. [PubMed: 23188670]
29. Einterz RM, Kimaiyo S, Mengech HN, et al. Responding to the HIV pandemic: the power of an academic medical partnership. Academic Medicine. 2007; 82(8):812–8. [PubMed: 17762264]
30. Inui TS, Nyandiko WM, Kimaiyo SN, et al. AMPATH: living proof that no one has to die from HIV. J Gen Int Med. 2007; 22(12):1745–50.
31. Tibshirani R. Regression shrinkage and selection via the LASSO. J Royal Statist Soc: Series B. 1996; 58(1):267–88.
32. Meier L, Van De Geer S, Buhlmann P. The group LASSO for logistic regression. J Royal Statist Soc: Series B. 2008; 70(1):53–71.
33. Bangsberg D, Hecht FM, Charlebois ED, Chesney M, Moss A. Comparing objective measures of adherence to HIV antiretroviral therapy: Electronic Medication Monitors and unannounced pill counts. AIDS Behav. 2001; 5(3):275–81.
34. Haberer JE, Kiwanuka J, Nansera D, Ragland K, Mellins C, Bangsberg DR. Multiple measures reveal antiretroviral adherence successes and challenges in HIV-infected Ugandan children. PloS one. 2012; 7(5):e36737. [PubMed: 22590600]
35. Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. The Journal of antimicrobial chemotherapy. 2004; 53(5):696–9. [PubMed: 15044425]
36. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clin Infect Dis. 2003; 37(8):1112–8. [PubMed: 14523777]
37. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. Clin Infect Dis. 2006; 43(7):939–41. [PubMed: 16941380]
38. Wilson IB, Bangsberg DR, Shen J, et al. Heterogeneity among studies in rates of decline of antiretroviral therapy adherence over time: results from the multisite adherence collaboration on HIV 14 study. J Acquir Immune Defic Syndr. 2013; 64(5):448–54. [PubMed: 24225904]
39. WHO Global Database on Child Growth and Malnutrition. Geneva: World Health Organization; 1997.
40. Marhefka SL, Farley JJ, Rodrigue JR, Sandrik LL, Sleasman JW, Tepper VJ. Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP). AIDS Care. 2004; 16(3):323–38. [PubMed: 15203426]
41. Katko E, Johnson GM, Fowler SL, Turner RB. Assessment of adherence with medications in human immunodeficiency virus-infected children. Pediatr Infect Dis J. 2001; 20(12):1174–6. [PubMed: 11740328]

42. Scanlon ML, Vreeman RC. Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings. HIV/AIDS Research and Palliative Care. 2013; 5:1–17.

43. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir Immune Defic Syndr. 2006; 43 (Suppl 1):S79–87. [PubMed: 17133207]

44. Bova CA, Fennie KP, Knafl GJ, Dieckhaus KD, Watrous E, Williams AB. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. AIDS Behav. 2005; 9(1):103–10. [PubMed: 15812617]

45. Muller AD, Bode S, Myer L, Roux P, von Steinbuchel N. Electronic measurement of adherence to pediatric antiretroviral therapy in South Africa. Pediatr Infect Dis J. 2008; 27(3):257–62. [PubMed: 18277933]

46. Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. The Annals of pharmacotherapy. 2001; 35(9): 1010–5. [PubMed: 11573846]

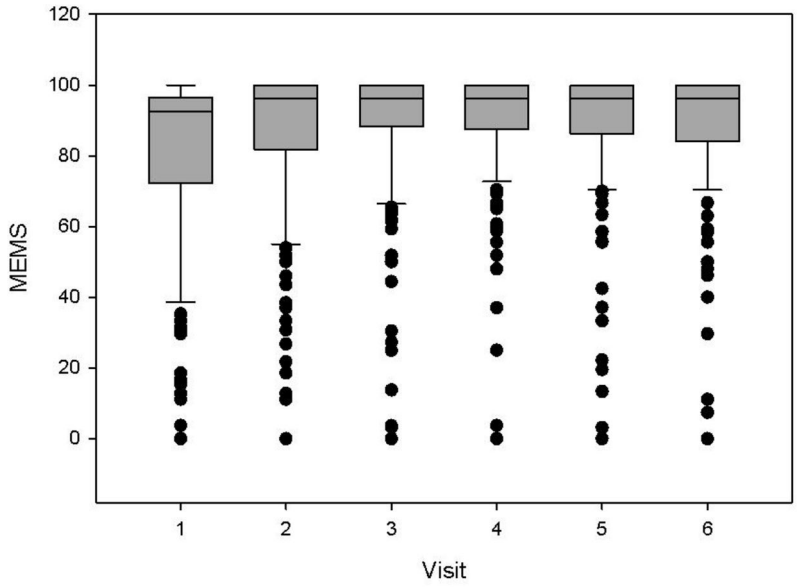

Figure I.
Adherence to ART by Medication Event Monitoring Systems

Table I

Study participants' characteristics

Child characteristics (N=191)	**Mean (Standard Deviation) or Frequency (%)**
Age (years)	8.2 (3.3)
Female	105 (55%)
Weight-for-age Z (WAZ) Score	−1.7 (1.3)
ART duration (years)	2.3 (1.9)
ART Regimen	
NVP	148 (77%)
EFV	43 (22%)
NVP/EFV (both)	2 (1%)
CD4%	26 (11)
WHO Stage (at baseline)	
1	34 (18%)
2	32 (17%)
3	104 (54%)
4	18 (9%)
Not answered	3 (2%)
Child disclosure status	
Child disclosed (knows HIV status)	44 (23%)
Caregiver characteristics (N=191)	Mean (Standard Deviation) or Frequency (%)
Caregiver relationship to child	
Mother	120 (63%)
Father	21 (11%)
Grandparent	13 (7%)
Non-related caregiver	7 (4%)
Sibling	3 (1%)
Other	27 (14%)
Caregiver employed outside the household	99 (52%)
Enrolled in AMPATH nutrition program	33 (17%)
Food insecurity (reported "not enough food for family in past 30 days")	134 (70%)
Difficulty with transportation to clinic	159 (83%)
Individuals reported as ever giving child medicines	
Mother	160 (84%)
Father	68 (36%)

Child characteristics (N=191)	Mean (Standard Deviation) or Frequency (%)
Sibling	80 (42%)
Relative (inside home)	68 (36%)
Child takes own medicine	60 (31%)

Table II

Discriminant Adherence Items as Indicated by Non-Zero Slopes in LASSO Selection by Visit

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Adherence Variable	**Item Number[a]**						
Variables significant at 2 or more visits							
Ever have problems keeping time with the medicines	12		−		−	−	
Currently enrolled in AMPATH nutrition program	17					+	+
Ever have problems getting child to take medicines	18		−		−	−	
How many doses of medicine has child missed in last month	23		−	−	−	−	
Child-level factors make it difficult to give medicines	24		−			+	−
Caregiver-level factors make it difficult to give medicines	25			−		−	
Number of days missed at least one dose in past week	34b					−	−
Number of days dose given more than one hour late in past week	34c		−	−	−		
Number of extra doses in past week	34f					−	−
Variables significant at only 1 visit							
Does child know taking medicines for HIV	9						−
Ever forget to keep time in giving the medicines	11						−
Ever not give medicines because don't want to give in front of others	13					−	
Does mother give the child the medicines	6						−
Community-level factors make it difficult to give medicines	26						−
Clinic-level factors make it difficult to give medicines	27		−				
Family-level factors make it difficult to give medicines	29						−
Number of missed doses in past week	34d					−	
Are there other children under 5 living in the household	36		−				
Demographic variables included for LASSO analyses							
Gender	n/a						−
Age (yrs)	n/a						
Duration on ART (yrs)	n/a			+			

NOTE: (+) or (−) denotes positive or negative slope value

[a] Refers to item number on Questionnaire included in Appendix 1

Table III

GEE model results for LASSO-selected items

Adherence Variable	Item Number	Odds Ratio	95% Confidence Interval
Ever have problems keeping time with the medicines	12	0.96	0.65–1.44
Currently enrolled in AMPATH nutrition program	17	0.50	0.22–1.10
Ever have problems getting child to take medicines[a]	18	0.43	0.22–0.83
How many doses of medicine has child missed in last month	23	1.15	0.87–1.52
Child-level factors make it difficult to give medicines	24	1.25	0.57–2.77
Caregiver-level factors make it difficult to give medicines[a]	25	2.20	1.06–4.56
Number of days missed at least one dose in past week[a]	34b	1.79	1.07–3.01
Number of days dose given more than one hour late in past week[a]	34c	1.26	1.08–1.47
Number of extra doses in past week	34f	1.04	0.81–1.33
Demographic variables included for multivariate analyses			
Gender	n/a	1.16	0.84–1.60
Age (yrs)	n/a	0.99	0.85–1.15
Duration on ART (yrs)	n/a	1.09	1.00–1.19

[a] Variable significant in multivariate regression $p<.05$

Table IV

Caregiver- and child-level barriers

Caregiver-level barriers	
25. Sometimes, a child does not take their medicines every day or at the same time every day because of difficulties for the caregiver. I am going to read a list of issues that may be problems for you as a caregiver in having the child take the medicines. Stop me when you hear a problem mentioned that applies to you.	
☐ I had difficulty with reading instructions	☐ I thought other matters were more urgent
☐ I did not understand the medication instructions	☐ I was away from home (work, field, etc.)
☐ I thought treatment was completed	☐ I was discouraged or losing hope
☐ I was not always around with the child	☐ There were frequent changes in caregivers
☐ I was taking alcohol or other drugs	☐ Caregiver being too busy and forgetting
☐ I did not want others to see	☐ I was not aware of child's status
☐ I had trouble with timing or giving the doses on time	☐ I wanted to try another treatment or prayers
☐ I did not think the drugs were helping	☐ Other (specify)
☐ I thought child needed a break from the medicines	☐ None of the above
☐ I was afraid of side effects on child	
Child-level barriers	
24. Some families tell us that their child worries them or makes it difficult to give them the medicines. Has your child not taken medicines for any of these reasons:	
☐ He/she does not know why taking the medicines or keeps asking questions about the medicines	☐ Can't take without food
☐ He/she did not understand the medication instructions	☐ He/she forgot to take medicine
☐ He/she was playing or at school or work	☐ He/she refused to take medicine
☐ He/she felt ill or was vomiting	☐ He/she felt better
☐ He/she does not want others to see the medicines	☐ He/she believes medicine does not help
☐ He/she had harm or side effects caused by the drugs	☐ Has problems with 1 formulation (tablets, liquids)
☐ Finds medicines too bitter	☐ Other (specify)
☐ He/she is tired of taking the medicines	☐ None of the above