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

Rachel C. Vreeman^{1,2,3}, Winstone M. Nyandiko^{2,4}, Hai Liu⁵, Wanzhu Tu⁵, Michael L. Scanlon^{1,2}, James E Slaven⁵, Samuel O. Ayaya^{2,4}, and Thomas S. Inui^{2,3,6}

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

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

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

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

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

⁶Department 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.

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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 $\geq 90\%$ 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 MEMS adherence ($\geq 90\%$ 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.

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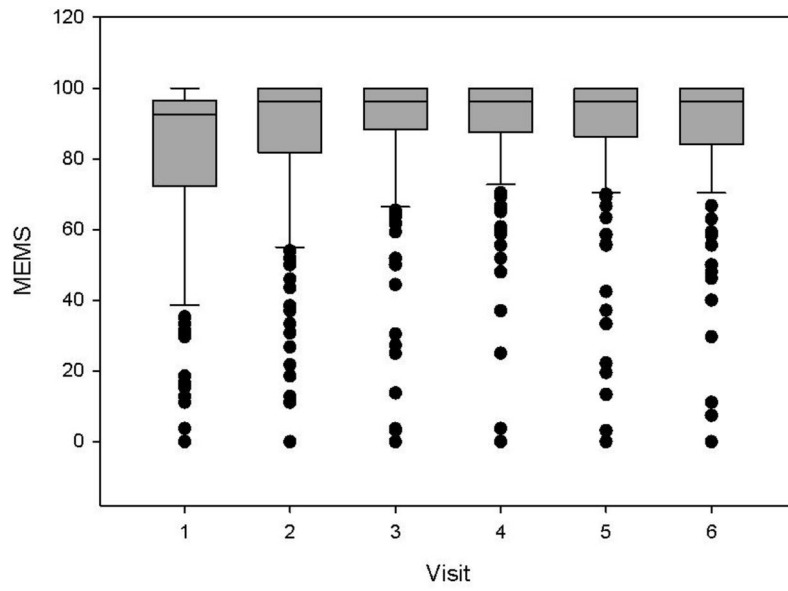


Figure I.
Adherence to ART by Medication Event Monitoring Systems

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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%)

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

Adherence Variable	Item Number ^d	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
<i>Variables significant at 2 or more visits</i>							
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					-	-
<i>Variables significant at only 1 visit</i>							
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

1
Refers to item number on Questionnaire included in Appendix

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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

^aVariable significant in multivariate regression $p < .05$

Table IV

Caregiver- and child-level barriers

<i>Caregiver-level barriers</i>	
<i>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>	
<input type="checkbox"/> I had difficulty with reading instructions	<input type="checkbox"/> I thought other matters were more urgent
<input type="checkbox"/> I did not understand the medication instructions	<input type="checkbox"/> I was away from home (work, field, etc.)
<input type="checkbox"/> I thought treatment was completed	<input type="checkbox"/> I was discouraged or losing hope
<input type="checkbox"/> I was not always around with the child	<input type="checkbox"/> There were frequent changes in caregivers
<input type="checkbox"/> I was taking alcohol or other drugs	<input type="checkbox"/> Caregiver being too busy and forgetting
<input type="checkbox"/> I did not want others to see	<input type="checkbox"/> I was not aware of child's status
<input type="checkbox"/> I had trouble with timing or giving the doses on time	<input type="checkbox"/> I wanted to try another treatment or prayers
<input type="checkbox"/> I did not think the drugs were helping	<input type="checkbox"/> Other (specify)
<input type="checkbox"/> I thought child needed a break from the medicines	<input type="checkbox"/> None of the above
<input type="checkbox"/> I was afraid of side effects on child	
<i>Child-level barriers</i>	
<i>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:</i>	
<input type="checkbox"/> He/she does not know why taking the medicines or keeps asking questions about the medicines	<input type="checkbox"/> Can't take without food
<input type="checkbox"/> He/she did not understand the medication instructions	<input type="checkbox"/> He/she forgot to take medicine
<input type="checkbox"/> He/she was playing or at school or work	<input type="checkbox"/> He/she refused to take medicine
<input type="checkbox"/> He/she felt ill or was vomiting	<input type="checkbox"/> He/she felt better
<input type="checkbox"/> He/she does not want others to see the medicines	<input type="checkbox"/> He/she believes medicine does not help
<input type="checkbox"/> He/she had harm or side effects caused by the drugs	<input type="checkbox"/> Has problems with 1 formulation (tablets, liquids)
<input type="checkbox"/> Finds medicines too bitter	<input type="checkbox"/> Other (specify)
<input type="checkbox"/> He/she is tired of taking the medicines	<input type="checkbox"/> None of the above