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Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP)

S. L. MARHEFKA,^{1,2*} J. J. FARLEY,¹ J. R. RODRIGUE,²
L. L. SANDRIK,³ J. W. SLEASMAN^{4†} & V. J. TEPPER¹

¹University of Maryland School of Medicine, ²University of Florida, College of Health Professions, ³University of Florida Health Science Center, Jacksonville & ⁴University of Florida, College of Medicine, Florida, USA

Abstract *This paper presents findings of a multi-site study designed to document: (1) caregivers' regimen knowledge; (2) barriers to adherence; and (3) the relationships between adherence, regimen knowledge and barriers. Fifty-one predominately female, African American parents and caregivers of HIV-infected children completed the Treatment Interview Protocol (TIP), a brief, structured interview designed to assess regimen knowledge and barriers to adherence. TIP data were compared to information obtained from medical records and pharmacy refill histories. Forty-nine per cent of children were considered adherent, defined as $\geq 90\%$ refill rate, which was significantly associated with virologic response. Significant regimen knowledge deficits were observed among caregivers, and inaccurate identification of prescribed medications was significantly associated with adherence. Caregivers identified 21 barriers to adherence, and poor adherence was significantly related to the number of barriers reported. Results indicate that the TIP is a successful tool for identifying regimen knowledge, potential adherence barriers and adherence problems. Results suggest that the TIP could be integrated into clinical practice as a quick, effective tool to identify poor adherers and guide interventions and treatment decision making.*

Introduction

As antiretroviral therapy (ART) has begun to slow disease progression and increase life span, the issue of adherence to medication treatment has become more salient. Researchers have suggested that: 'the key to success of the new regimens is the ability and willingness of HIV-positive individuals to adhere to complex antiretroviral regimens, perhaps for life' (Friedland

Address for correspondence: Stephanie Marhefka, PhD, 550 1st Avenue, NBV8W5I, New York, NY 10016, USA. E-mail: Stephanie@marhefka.net

* S. L. Marhefka is now at New York University School of Medicine.

† J. W. Sleasman is now at the University of South Florida, College of Medicine.

& Williams, 1999). In fact, studies have suggested that 90–95% adherence is necessary for viral suppression, and that moderate rates of adherence may be harmful (Bangsberg *et al.*, 2000; McNabb *et al.*, 2001; Paterson *et al.*, 2000). Despite the importance of adherence among children on ART, relatively few studies have examined adherence levels among children in this population (Farley *et al.*, 2003; Reddington *et al.*, 2000; Steele *et al.*, 2001; Van Dyke *et al.*, 2002; Watson & Farley, 1999).

Only one known study has assessed caregiver knowledge of children's prescribed ART medication regimens as it relates to adherence. Katko *et al.*, (2001) asked 35 caregivers to name or describe their children's ART medications and corresponding dosages and dosing frequencies. Nineteen (54%) of the caregivers provided accurate medication information; of those, 12 had pharmacy refill ratings of 90% adherence or better, while none of those who lacked knowledge of the regimen had 90% adherence ratings or higher. This study was limited by a small sample size and only one method of adherence assessment, yet the study is important as it supports the use of knowledge assessment as an indicator of adherence.

Reddington and colleagues (2000) examined adherence via self-report interview with caregivers of HIV-infected children. Thirty-nine of 90 caregivers (43%) reported that the target child missed at least one dose in the previous week. Based on viral load data, the recall of missed doses designated adherence with good sensitivity (70%) and moderate specificity (57%), and detected non-adherence with moderate positive predictive value (50%). Sixty-two per cent of caregivers were appropriately categorized as adherent or non-adherent using this method. In a larger study, Van Dyke and colleagues (2002) assessed adherence among 125 children (ages four months to 17 years) on ART using the Pediatric AIDS Clinical Trial Group (PACTG, no date) Pediatric Adherence Questionnaire Modules 1 and 2 (<http://www.fstrf.org/qol/peds/pedadhere.html>). Eighty-eight per cent of respondents were caregivers, while 12% of the respondents were children who were primarily responsible for administering their own ART. Thirty per cent of respondents reported that the child had missed at least one dose in the prior three days. Based on viral load data, the recall of missed doses designated adherence with low to moderate sensitivity (43.6%) and moderate positive predictive value (68%), and detected non-adherence with moderate specificity (63.5%). Fifty-one per cent of caregivers were accurately categorized as adherent or non-adherent using this method. Taken together, these results suggest that recall of missed doses does correctly identify many adherers, though this method may incorrectly categorize up to half of caregivers as adherent or non-adherent.

Although some studies have supported the use of 3–7 day self-report recall of medication administration, two recent studies were unable to replicate these findings. Steele and colleagues (2001) used the PACTG modules (with caregiver self-report) and pill count to measure adherence among 30 children on ART; electronic monitoring data was also available for eight of the 30 children. None of the adherence measures were significantly correlated with viral load. Self-report overestimated adherence ($M = 94.3\%$) when compared to pill count ($M = 89.9\%$) and electronic monitoring ($M = 44.9\%$). Farley and colleagues (2003) replicated these findings. They found that among 26 children less than 13 years old, median adherence ratings were: 100% based on the PACTG self-report measure, 81% based on electronic monitoring and 79% based on pharmacy refills. Electronic monitoring data and pharmacy refill data were both significantly related to viral load. Combined, the results of these studies suggest that the PACTG adherence measure may overestimate adherence and lack convergent validity. However, the results provide moderate support for the validity of adherence assessment with electronic monitoring and pharmacy refill histories.

The pharmacy refill history is particularly interesting for clinicians, as pharmacy refill histories are relatively inexpensive to obtain, and studies have generally found that pharmacy

refill rates are closely associated with viral load. Watson and Farley (1999) examined adherence with pharmacy refills among 72 children ages 3 months to 12 years. Children who were deemed $>75\%$ adherent to refill were significantly more likely to have a viral load ≤ 400 than those who were deemed $<75\%$ adherent. Katko and colleagues (2001) found that among 35 children on ART, those who were at least 90% adherent to refill were significantly more likely to show a virologic response than those who were less adherent.

The reviewed studies suggest that regimen knowledge assessment and the pharmacy refill history may be the best methods available for adherence assessment within the clinical setting. However, like the recall of missed doses, these methods are imperfect. The pharmacy refill method provides no confirmation of medication consumption, of whether or not the medication was taken at appropriate times, or of whether or not the dietary requirements for proper absorption were met. The knowledge assessment helps to clarify whether or not inaccurate knowledge may contribute to non-adherence, but fails to provide information about everyday barriers to adherence.

Asking about barriers may be essential to the clinical assessment of adherence. Clinicians must identify and understand the obstacles to adherence if they plan to partner with children and their families with the goal of increasing adherence. The current standard for barrier assessment is a close-ended barrier checklist that has not been validated by comparison with a qualitative assessment of barriers experienced by children and their families, and has not been validated by comparison with other adherence measures (Farley *et al.*, 2003; Reddington *et al.*, 2000; Steele *et al.*, 2001; Van Dyke *et al.*, 2002). Thus, an extensive qualitative examination of the barriers facing these families is necessary.

In the present study a new caregiver self-report assessment tool (the Treatment Interview Protocol; TIP) was evaluated and compared with a more objective and global measure of adherence (Pharmacy Refill Rate). Information was gathered regarding the extent to which children were reportedly receiving their medications at the prescribed dosing intervals (Interval Deviance), the extent of caregivers' knowledge of their children's prescribed ART regimens (Identification of Prescribed Medications, Knowledge of Prescribed Dosing Amount, Knowledge of Medication-Specific Dietary Requirements) and Barriers to Adherence. It was hypothesized that Pharmacy Refill Rate would significantly and negatively relate to Viral Load, caregivers' ability to identify their children's prescribed medications would relate significantly and positively to Pharmacy Refill Rate, and that the number of Barriers to Adherence caregivers reported during the TIP would significantly and negatively relate to Pharmacy Refill Rate.

Methods

Procedure

At each study site, the research nurse helped the study recruiter/interviewer complete the eligibility checklist for each potential participant. The recruiter/interviewer then asked eligible caregivers several questions to ensure that eligibility criteria were met. Eligible participants underwent informed consent procedures in accordance with local IRB approval at each study site. After completing informed consent procedures, caregivers were administered the TIP by trained undergraduate psychology students or graduate students in clinical psychology. All interviewers were Caucasian and had no previous relationship with participants. Interviewers were required to undergo training for administering the TIP before conducting interviews for the study. Interviewer training involved general education about reflective listening, practising administration of the TIP, and successfully administering the TIP to the principal

investigator. Following the TIP, a demographic questionnaire was completed with the caregivers and a medical record abstraction was completed. Three months following the enrollment visit, pharmacies were contacted to obtain pharmacy refill histories for the prior three months.

Measures

Treatment Interview Protocol (TIP). This caregiver-completed structured interview was designed by the primary author to assess typical adherence to prescribed regimens, understanding and knowledge of the prescribed regimen, and barriers to adhering to each aspect of the paediatric ART regimen. The measure was adapted from the Treatment Adherence Questionnaire, which is used to assess adherence to paediatric cystic fibrosis regimens (Quittner *et al.*, 2000).

Throughout this study, the average administration time for the TIP was 9.5 minutes (range = 4–19 minutes). Administration times varied based on the regimen knowledge level of the caregivers, the number of medications in a regimen and the extent to which caregivers were inclined to provide extraneous information. In order to promote honest responding, the interviewer first collects information about the *actual* regimen behaviours that were typically conducted within the past two weeks, making sure to avoid evaluative or judging statements. Next, the interviewer asks the informant to recall the recommended or prescribed regimen. The question sequencing is meant to indirectly give the caregiver permission to be truthful about discrepancies between actual behaviour and the prescribed regimen (see the Appendix for the interview script).

The interviewer uses a display card to aid the caregiver in identifying medications and dosing amounts. The display card includes pictures of all ART medications and corresponding medication names (generic and brand), to help those who may be familiar with the appearance of the medications but may not know the medication names. The display card also includes sample syringes to aid the caregiver in communicating the dosing amounts for liquid formulations.

TIP part I: typical regimen behaviour. The interviewer begins by asking the caregiver to state the ART medications that the child has typically taken to treat his or her illness within the last two weeks. Part I yields one variable relevant to the present study: Typical Dosing Interval. During the interview the caregiver states the times during the day at which the target child typically received each medication in his or her regimen. For twice daily medications, Typical Dosing Interval is the number of hours between the two dosing times stated by the caregiver. For thrice daily medications, two Typical Dosing Intervals are computed (Interval 1: 3rd dose time–2nd dose time; Interval 2: 2nd dose time–1st dose time). Typical Dosing Intervals are used to compute the Interval Deviance score. Interval Deviance is the absolute value of the number of hours that a reported interval varied from the prescribed interval (number of hours in prescribed interval–number of hours in Typical Dosing Interval). In the present study more than 45 minutes before or after an hour was rounded to the next hour. Interval Deviance scores were not computed for once daily dosing, as the interview provided only one data point for dosing times of once daily medications.

TIP part II: knowledge of the prescribed regimen. After completing Part I, the interviewer asks the caregiver to verbally list the ART medications the doctor prescribed for the child to take within the previous two weeks, as well as the prescribed dosing interval, the prescribed dosing amount and special instructions about food and drink intake pertaining to each

prescribed medication. As with Part I, a display card is available in order to aid caregivers in medication identification. Informants are also asked to list the barriers to the child's adherence that the child or family experienced within the past two weeks. Resulting variables from Part II include Identification of Prescribed Medications (percentage of medications accurately identified), Frequency Knowledge (percentage of dosing frequencies accurately identified), Knowledge of Dosing Amount (percentage of medications for which dosage amount is accurately identified), Knowledge of Medication-Specific Dietary Requirements (percentage of medications for which dietary requirements are accurately identified) and Barriers to Adherence (recorded verbatim).

Pharmacy refill history

During the informed consent process, caregivers provided the researcher with information regarding the pharmacies at which they refill prescriptions for their children and granted permission for the researchers to contact the pharmacies and obtain pharmacy refill information. Pharmacies were provided with copies of the pharmacy record release forms, and three-month pharmacy refill histories were obtained. Pharmacy Refill Rates were calculated by dividing the number of doses expected for each medication during a three-month period by the number of doses filled at the pharmacies over that period. Values greater than one were scored as 100% adherent.

Virologic data

Viral load results were obtained via chart abstraction. All sites obtained viral load results clinically at least once every three months for each patient. Sites employed the Roche Amplicor reverse transcribed-PCR method either standard (400 copy/ml. lower threshold) or the ultra-sensitive (50 copies/ml. lower threshold) assays.

Data analyses

Data were analyzed using the Statistical Package for Social Sciences, Version 10.05 (SPSS 10.05). First, descriptive data were reviewed. Barriers to Adherence were recorded verbatim and categorized by the author. Pharmacy Refill Rate data were viewed continuously and then the correlation between Pharmacy Refill Rate and viral load was examined. Pharmacy refill data were then split at a threshold of 90%, based on the research literature (Bangsberg *et al.*, 2000; McNabb *et al.*, 2001; Paterson, 2000). Chi-square analyses were conducted to examine the relationship between pharmacy refill rate and viral load (≤ 400 copies/ml versus > 400 copies/ml), in order to validate the pharmacy refill history as a measure of adherence. Correlational analyses were completed to examine the continuous relationships between Pharmacy Refill Rate and both Identification of Prescribed Medications and number of Barriers to Adherence. Chi-square analysis was employed to test for a relationship between Pharmacy Refill Rate ($\geq 90\%$ versus $< 90\%$) and Identification of Prescribed Medications (100% versus $< 100\%$ accurate identification).

Results

Participants

To be eligible for the study, a child's caregiver must have: (1) considered herself or himself to be the primary person responsible for the child's medication-taking; and (2) reported that

English was her or his primary language. Several eligibility requirements were determined to ensure that the designated caregiver would be able to respond to questions about the child pertaining to the month immediately before and the month immediately following enrollment. The target child must have been between the ages of 2–12 years at the time of enrollment and must have been living with the caregiver during the previous month. To control for specific issues related to adjusting to new regimens, the child must have been prescribed the same antiretroviral medication(s) for the past three months. Children who did not plan to live with the caregiver for the preceding three months and children in foster care were excluded from the study because a change of primary caregiver during the study period could impact the pharmacy refill process and render the Pharmacy Refill Rate a less valid indicator of adherence. Children concurrently enrolled in an adherence intervention study were excluded from participation in this study due to concerns about cross-over effects. Siblings of enrolled children were excluded from participation in order to keep the observations independent from one another.

Study participants were parents or primary caregivers of perinatally HIV-infected children ages 2–12 years, who were receiving their care at urban, public, university-affiliated, Pediatric AIDS Clinical Trials Group (PACTG)-affiliated paediatric HIV speciality clinics in Gainesville, Florida, Jacksonville, Florida, and Baltimore, Maryland. Seventy-three caregivers met eligibility criteria and were invited to participate in the study. Sixty-three primary caregivers (86%) consented to participate. Twelve participants were omitted from the analyses due to problems obtaining pharmacy refill data, leaving a total of 51 participants with both interview and pharmacy data, including 14 from the Gainesville site, 18 from the Jacksonville site and 18 from the Baltimore site (see Table 1). Caregivers who declined or dropped out from the study did not differ from completers at the individual sites in terms of demographic characteristics or the proportion of children with viral load below the limits of detection at the time of enrollment.

Validation of pharmacy refill rate

The relationship between Pharmacy Refill Rate and virologic data was examined in order to determine the validity of the Pharmacy Refill Rate as a measure of adherence. The correlation between Viral Load and Pharmacy Refill Rate approached significance ($r = -0.27$, $p = 0.06$), suggesting a trend toward children with lower viral loads having higher Pharmacy Refill Rates. When participants were categorized as 'adherent ($\geq 90\%$ refill rate)' and 'non-adherent ($< 90\%$ refill rate)', Viral Load was significantly related to Pharmacy Refill Rate ($\chi^2 = -4.40$, $p < 0.05$). Pharmacy Refill Rate correctly identified 16 out of 25 children as adherent (sensitivity = 64%) and correctly identified 17 out of 26 as non-adherent (specificity = 65%). Of the 25 who were identified as adherent, 16 were actually adherent, defined as having a Viral Load ≤ 400 copies/ml (predictive value = 64%). Based on this validation, good adherence was defined as $\geq 90\%$ Pharmacy Refill Rate for the following analyses.

Identification of prescribed medications

Caregivers' Identification of Prescribed Medications during the TIP ranged from 0% to 100% accuracy, with a mean of 86% accuracy (SD = 0.27). A majority (62%) of participants used some cue to identify their children's medications: 33% of caregivers consulted their own lists of the children's medication information and 29% consulted the medication display card. Thirty-six caregivers (71%) were able to correctly identify all of their children's medications

Table 1. Participant demographic information

Variable	Percentage/mean (SD) for children (<i>n</i> = 51)	Percentage/mean (SD) for caregivers (<i>n</i> = 51)
Age	8.76 (3.06)	45.17 (13.14)
Gender (%)		
Female	47.1	88.2
Ethnicity (%)		
African American	82.4	70.6
Caucasian	9.8	21.6
Other	7.9	7.9
Knowledge of own HIV status (%)	56.9	29.4
Years prescribed ART	6.94 (3.04)	–
Caregiver relationship (%)		
Biological parent	–	41.2
Biological grandparent	–	19.6
Adoptive parent	–	29.4
Other relative/family friend	–	9.8
Caregiver marital status (%)		
Single	–	33.3
Married	–	41.2
Separated or divorced	–	15.7
Widowed	–	7.8
Caregiver education (%)		
Grade school	–	3.9
Some high school	–	27.5
Graduated high school/earned GED	–	37.3
At least some college	–	31.4
Caregiver employment status (%)		
Employed full-time	–	35.3
Employed part-time	–	9.8
Unemployed	–	9.8
Disabled or retired	–	25.4
Homemaker	–	19.6
Yearly household income	–	\$22, 804 (\$15,301)

with or without aid. Identification of Prescribed Medications was significantly and positively correlated with Pharmacy Refill Rate ($r = 0.34$, $p < 0.01$), such that caregivers with more accurate Medication Identification tended to have higher Pharmacy Refill Rates. When the data was split based on 100% versus < 100% Identification of Prescribed Medications and $\geq 90\%$ versus < 90% Pharmacy Refill Rate, accurate identification of all ART medications significantly and positively predicted Pharmacy Refill Rate ($\chi^2 = 7.16$, $p < 0.01$). Caregivers with $\geq 90\%$ Pharmacy Refill Rate were more likely to correctly identify all of their children's medications than caregivers with < 90% Pharmacy Refill Rate. Overall, Identification of Prescribed Medications correctly identified 67% of children as either adherent or non-adherent. Identification of Prescribed Medications correctly identified 22 out of 25 children as adherent (sensitivity = 88%) and correctly identified 12 out of 26 as non-adherent (specificity = 46%). Of the 36 who were identified as adherent, 22 were actually adherent, defined as having a $\geq 90\%$ Pharmacy Refill Rate (predictive value = 64%).

Specific dosing instructions

Only one caregiver was unable to correctly identify the prescribed medication-taking frequency for her child's known medications. When the medications were accurately identified by the caregivers, the percentage of medication dosing amounts accurately reported by caregivers ranged from 0% to 100%, with a mean of 83% (SD = 0.31). Twenty-seven out of 36 caregivers (75%) correctly identified the dosing amounts for all of their children's ART medications. Of the 31 whose children were prescribed medications with specific dietary requirements, 14 (45%) caregivers correctly identified all of the specific dietary requirements associated with their children's medications. Caregiver reports indicate that in the previous two weeks 17.3% of prescribed twice-daily doses and 58.4% of prescribed thrice-daily doses were typically taken two or more hours earlier or later than the prescribed dosing intervals. Refer to Table 2 for Interval Deviance descriptive data.

Barriers

Caregivers reported an average of 0.90 barriers to their children's adherence (SD = 1.19; Table 3). Barriers to Adherence were significantly and negatively correlated with Pharmacy Refill Rate ($r = -0.307$, $p < 0.05$). Caregivers who reported more barriers to adherence tended to have children with lower Pharmacy Refill Rates.

Discussion

This study demonstrates that the TIP, a brief structured caregiver-completed interview, measures medication regimen knowledge, medication administration practices and barriers to adherence. The study also shows that the TIP provides a valid means of predicting adherence. TIP Identification of Prescribed Medications was significantly correlated with adherence, meaning that caregivers who were more accurate in identifying their children's medications tended to be more adherent. This finding corroborates the results of another study of regimen knowledge among caregivers of infected children (Katko *et al.*, 2001), which suggested that regimen knowledge is associated with adherence. Together, the two studies suggest that it may not be necessary to test medication knowledge experimentally or with expensive technology (e.g., the Pills Identification Test (PIT); Parienti *et al.*, 2001) because asking about knowledge explicitly during an interview and using a standard medication chart as a reference is an effective means of identifying regimen knowledge deficits.

Although categorizing caregivers based on 100% versus < 100% medication identification detected adherence with very good sensitivity, the TIP demonstrated poor specificity; it appropriately categorized only about half of non-adherent children. This finding suggests that if the TIP is used as the sole clinical measure of adherence, many non-adherent caregivers

Table 2. *Percentage of typical doses deviant from prescribed intervals*

Deviance amount	% of twice-daily doses ($n = 128$)	% of thrice-daily doses ($n = 24$)
Less than 1 hour	57.0	29.2
1–2 hours	25.8	12.5
2–3 hours	10.2	16.7
3–4 hours	5.5	29.2
≥ 4 hours	1.6	12.5

may go undetected. Finding a specific measure of ART adherence in paediatric populations is not easy, as both the three-day (Van Dyke *et al.*, 2002) and seven-day recall of missed doses (Reddington *et al.*, 2000) have demonstrated only slightly greater specificity (63.5 and 56.8, respectively). A combination of self-report (via the TIP or recall of missed doses) and pharmacy record review may be the most effective means of clinically evaluating whether or not children are receiving their medicine.

The TIP not only helps to identify some non-adherers, it also shows that many caregivers who can successfully identify the medications may not know the prescribed dosing amounts or the specific dietary requirements associated with their children's prescribed medications. Furthermore, the TIP suggests that many children may be receiving their ART at dosing intervals that are significantly deviant from those prescribed, particularly when medications are prescribed to be taken thrice daily. The knowledge deficits found in this study point to the need for improved education and counselling in the clinical setting. Caregivers' inability to accurately identify the medication-specific dosing and dietary requirements may be, in part, attributable to inadequate education and counselling. It is difficult to ascertain the

Table 3. Comparison between PACTG barrier checklist items and TIP-reported barriers

PACTG module 2 barrier checklist	TIP-reported barriers (number of caregivers who reported barrier)
A. Can't get drug (drug store doesn't have supply)	<ul style="list-style-type: none"> • Pharmacy does not always have medicine in stock (1)
B. Didn't refill; ran out	<ul style="list-style-type: none"> • I have difficulty travelling to get the refills (1) • I have difficulty getting the refill (no reason stated; 1)
C. Taste, can't get it down, spits up, amount (pills or liquid)	<ul style="list-style-type: none"> • Pills are too big to swallow (5) • Medication tastes bad (5) • Too many pills (3) • Can't keep the medicine down (1) • Child isn't able to swallow pills (1) • Child doesn't drink all of the medicine (1)
D. Forgot	<ul style="list-style-type: none"> • Child or family forgets (4) • I have difficulty remembering to take the medicine when we go out (1) • I have difficulty keeping up with dosing times/ intervals (1)
E. Side effects/toxicity	<ul style="list-style-type: none"> • Side effects (2)
F. Scheduling—interferes with lifestyle (meals, school, sleep)	<ul style="list-style-type: none"> • Medication-taking interferes with daily activities (2)
G. Child refuses	<ul style="list-style-type: none"> • Child avoids, resists, prolongs or refuses the medication (7)
H. Multiple caretakers	
I. Concerns about disclosure	<ul style="list-style-type: none"> • I worry that others will find out about my child's status (1)
J. Intercurrent illness	<ul style="list-style-type: none"> • Child has difficulty with the medicine when he/she is sick (2)
K. Other	<ul style="list-style-type: none"> • Child needs parental supervision/reminding (2) • Child hides the medicine (1) • Child wants to be normal (1) • I have difficulty preparing the solution (1)

importance of the specific dietary and dosing interval requirements, as our knowledge of their effects is imperfect and the impact of non-adherence to these requirements likely varies among medications. However, as long as medication-specific dietary and dosing interval requirements are deemed important, care teams have a duty to educate caregivers and children about them. For example, providers would be wise to tell caregivers that each dose should be taken 12 hours apart instead of telling them that the medication should be taken twice a day. It is important for health care teams to educate caregivers and children about the specific dosing requirements and the importance of maintaining dietary requirements and dosing intervals, partner with the caregivers to schedule medication-taking into the children's and caregivers' daily routines, and work collaboratively to alter regimens as needed. These quick interventions will help to make medication taking easier for families, and will help to eliminate dosing administration problems.

Another important finding of this study is that the open-ended barrier assessment within the TIP appears to be useful in identifying barriers to adherence. The 51 caregivers in the present study made 44 barrier disclosures and identified a total of 21 barriers to adherence. The barriers reported in the current study generally fell into one of the following categories: (1) medication attributes; (2) conflict between children and caregivers; and (3) behavioural/psychological difficulties. Caregivers who reported higher numbers of barriers were somewhat more likely to have children with lower Pharmacy Refill Rates, which suggests that interventions aimed towards eliminating barriers may be effective in increasing ART adherence.

The barrier assessment in this study differs from barrier assessments in other studies of paediatric ART adherence in that an open-ended interview format was used rather than a checklist that bore a predetermined list of barriers. The barriers reported here are generally similar to the barriers listed in the PACTG Adherence Module 2 (Table 3); though the barriers reported in this study tend to be more specific than the barriers in the PACTG checklist, and several unique barriers were reported in this study (e.g. 'child hides the medicine', 'child needs parental supervision/reminding', 'child wants to be normal' and 'I have difficulty preparing the solution'). For clinical use, one might consider continuing to use the current PACTG checklist, and asking additional questions when an item is endorsed. For example, if a caregiver endorses 'Didn't refill; ran out', the interviewer may ask: 'Did you forget to call the pharmacy, did you have a hard time getting to the pharmacy, or was there another reason that you ran out of medication?' One risk of that approach is that someone may fail to endorse the initial item, even though they experience a related barrier. For example, during the TIP, a caregiver reported that the child 'puts off' taking the medicine. The caregiver might not think that qualifies as 'child refuses,' and, therefore, might not endorse 'child refuses' as a barrier. That caregiver probably would endorse 'child avoids, resists, prolongs or refuses the medication'. Therefore, researchers may wish to use the barriers reported in this study to revise the current PACTG checklist or to develop a new, slightly longer, more detailed, more child-specific barrier checklist. Similarly, researchers developing future self-report checklists might consider using a qualitative method like that used in this study.

Limitations

This study was limited by several factors. First, children in foster care were excluded from participation, therefore, the results may not generalize to children in foster care settings. Second, only primary caregivers served as informants in this study. In the future, it may be helpful to include children and other integral caregivers in the interview. A third limitation is that the Interval Deviance variable may not accurately reflect the daily dose timing, as the

variable is derived from a question about the *typical* times at which the medication was taken *over a two-week period*. A diary or recall interview method may yield more accurate information about deviance from prescribed dosing times. However, the Interval Deviance results from the current study remain noteworthy. If it is assumed that caregivers responded in accordance with some social desirability, then the results suggest that caregivers may lack knowledge about the best dosing intervals. Alternatively, if it is assumed that caregivers responded by averaging the times at which their children receive the medication, then the results suggest that, on average, a significant number of doses are administered outside of the recommended intervals. The literature has given little attention to children's adherence to the dosing intervals prescribed for their ART, therefore the current results are an important addition to the literature. The Interval Deviance results of the present study should alert health care teams to possible problems with dose timing but should not be over-interpreted.

A third limitation of the study involves the use of Pharmacy Refill Rate as a measure of adherence. Unfortunately, there is no gold standard for medication adherence assessment. Pharmacy Refill Rate was chosen as the primary measure of adherence in this study because it is an objective measure of adherence, studies have generally supported the convergent validity of this method and pharmacy refill information is much less expensive than electronic monitoring. Nevertheless, Pharmacy Refill Rate is an imperfect method of measuring medication adherence; it measures the extent to which medications were filled by pharmacies but, like other methods of adherence assessment, fails to provide any assurance that the medication was actually consumed by the target child. This method may underestimate adherence in cases in which the families have additional medication supplies at home. In this study underestimation of adherence also may have occurred if some families switched pharmacies during the study period and failed to inform the study staff of that change. Despite these limitations of the pharmacy refill approach, this study supported the convergent validity of the pharmacy refill method.

A final limitation involves the assessment of adherence barriers. Although the open-ended barrier assessment is a strength of the current study, the phrasing of the barrier question involves providing some examples of barriers, which may have served as a *de facto* barrier checklist. In fact, the top four barriers listed by caregivers were referenced in the interview question, suggesting that these barriers may have been reported most frequently because of the wording of the question. Furthermore, while the open-ended barrier assessment used in this study may be helpful in the revision or development of barrier checklists, a close-ended barrier checklist format may be a more effective long-term strategy for assessing barriers, as barrier checklists can be standardized, they produce quantitative data that are easier to analyze than qualitative data, and they involve recall, which tends to be easier than recognition.

Strengths

The present study makes a strong contribution to the literature regarding adherence to ART. The promising new method of clinical adherence assessment that is introduced in this study varies from the current standard of focusing on adherence failure or missed doses. Instead of challenging a caregiver's ability to execute the regimen, the TIP offers a means of assessing adherence while partnering with caregivers by attempting to understand their experiences with medication administration—focusing especially on the difficulties that they experience with the prescribed regimen.

The current study also adds to the literature by supporting the validity of several other adherence assessment methods. This study provides further validation of Pharmacy Refill

Table 4. *TIP-identified problems and suggested interventions*

Problems identified by the TIP	Potential implications	Suggested interventions
(1) Does not accurately identify the prescribed medications	Child may not be getting the medicine	<ul style="list-style-type: none"> ✓ Determine whether or not adherence is a problem <ul style="list-style-type: none"> – Examine viral load – Obtain pharmacy refill history (if available) – Ask the caregiver/child about missed doses ✓ If any corroborative data suggest that adherence is or may be a problem, talk with the caregiver about adherence concerns and make appropriate referrals (e.g. health educator, community health nurse home visits, pharmacy consultation, social work, psychologist, etc.)
(2) Does not accurately identify the frequency of dosing, dosing amounts and/or dietary requirements	Child may not be getting the proper amount of the medicine	<ul style="list-style-type: none"> ✓ Educate caregiver and child about the prescribed frequency, dosing amounts and/or dietary requirements and the importance of implementing these practices ✓ May provide information sheet with stickers or other aid to remind family of the frequency, dosing amounts and/or dietary requirements
(3) Interval deviance is high	Child may have inoptimal levels of medicine in the blood-stream during certain times	<ul style="list-style-type: none"> ✓ Educate caregiver and child about the prescribed dosing intervals and the importance of the child receiving the medications at those intervals ✓ Talk with caregiver and child about their daily routines and help them identify ways in which they can fit the medication administration into routines. Also help to identify cues or things that they do daily which can help them remember to administer the medication
(4) Caregiver and/or child identifies barriers	Child may not be consistently getting the medicine as prescribed	<ul style="list-style-type: none"> ✓ Address each barrier separately and work with the family to identify possible solutions

Rate as a measure of adherence by demonstrating a significant relationship between Pharmacy Refill Rate and Viral Load, even among a population of children who are not beginning a new HAART regimen, and for whom virologic suppression may not be a reasonable goal of therapy. Additionally, this study supports the convergent validity of the PACTG barrier assessment, in that the barriers reported in response to open-ended questions were generally similar to the barriers listed in the PACTG barrier checklist.

Integrating the TIP into clinical care

The TIP is a promising method for assessing adherence in clinical settings. The TIP provides valuable information about caregiver regimen knowledge deficits, administration problems

and barriers to adherence. Nurses, medical assistants or other members of the health care team can quickly administer this brief, structured interview to caregivers as part of routine clinical adherence assessment. Information resulting from the TIP can be used by care teams to correct knowledge deficits, to help the family eliminate or address barriers to adherence and to help physicians with clinical decision making regarding ART. Refer to Table 4 for a matrix of problems and suggested interventions.

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Appendix A: Treatment Interview Protocol (TIP) script

TIP part I

Thank you for agreeing to participate in this study. As we discussed during the informed consent process, we are trying to learn more about families with children who have illnesses like your child has. Today, I want to learn about what things are like in your family. Doctors often give children like yours many medications to take. But making sure that your child gets all the medications can be really hard, so families do the best that they can. Tell me, what has your family typically done to manage or treat _____'s illness in the past two weeks? Has _____ take any medications in the past two weeks?

If the caregiver answers yes: What medications has your child taken?

If the caregiver answers no, proceed to Section 2.

Mark the medications on the recording sheet. If the caregiver describes the medication(s), say: Do you know the name of it?

If the caregiver cannot recall the name, first say: We'll come back to that one. What other medications has your child taken?

When the caregiver can no longer name any medications, if some are left unnamed, then show the display card. If display card is used, mark DC on recording sheet. If subject uses notes to name medication at any time, mark CS (cheat sheet) for that medication. Otherwise, begin with the first medication, and say:

You said your child has taken _____, does that come in capsules, tablets, powder or liquid? **Record the response, then say:**

In the past two weeks, how many times a day has your child taken _____? **Record the response, then say:**

And at what times during the day has your child taken _____? **Record the response, then say:**

When your child has taken _____, how much has he/she taken? **Here, you want to know how many tablets or capsules, or how much powder or liquid.**

And who has been involved in that? **Record the response and provide the caregiver with encouragement that his/her responses are important and helpful. Then, go to the next medication on the list, and repeat this set of questions for each medication on the list.**

When you have queried all medications for typical medication-taking behaviours, you may want to provide a summary statement that lets the caregiver know that you realize that managing the medication taking must be difficult, and it sounds as if he/she is really trying hard (if appropriate).

TIP part II

Next, say: Now that I have learned all about the medications that _____ typically takes, I'd like you to tell me about the things your doctor, nurse or pharmacist told you to do. During your last clinic visit (before today), what medications did your doctor, nurse or pharmacist recommend that you give to your child?

Mark the medications on the recording sheet. If the caregiver describes the medication(s), say: Do you know the name of it?

If the caregiver cannot recall the name, first say: We'll come back to that one. What other medications has your doctor, nurse or pharmacist recommended?

When the caregiver can no longer name any medications, if some are left unnamed, then show the display card. Otherwise, begin with the first medication, and say:

Let's start with _____. How often did your doctor, nurse or pharmacist recommend that you give your child _____? **Record the response, and say:**

And how much did your doctor, nurse or pharmacist recommend that your child take each time? **Record the response, and say:**

Sometimes doctors, nurses and pharmacists give special instructions about how to take medications. For example, they might say take the medication with food, take it on an empty stomach, do not eat fatty foods with this medication, or give other instructions. What special instructions did you receive about giving your child _____? **Record the response, and say:**

Many different things can make it hard for children to get the medicines their doctors recommend. For example, sometimes the pills are too big for the children to swallow, they won't take the medication because it tastes bad or families sometimes forget about the medication. What kinds of things make it hard for your child to get _____ like the doctor recommended? **Record the response(s) and show the respondent the rating card. Ask the respondent:** How often does this happen? **And then:** How often does this problem keep your child from getting the medicine like the doctor recommended?

What other things keep your child from getting _____ when and how the doctor suggested? Record the response. **Now go to the next medication on the list and repeat this set of questions for each medication on the list.**

When you reach the end of the recommended medication list, say: The information you have given me will be very helpful. I am beginning to understand some of the things that make it hard for families with children who have HIV. Are there other things that keep your child from getting the medications the doctor recommended? **Record the response, and say:**

Thank you for providing that information. The information you have given me today has really helped me to learn more about what it is like for your family to manage _____'s illness. Thank you so much for helping us out! I have just a few more questions for you, and then we'll be through.

Note: Bold lettering indicates an instruction.