Reported Adherence as a Determinant of Response to Highly Active Antiretroviral Therapy in Children Who Have Human Immunodeficiency Virus Infection

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ABSTRACT. Objective. The complexity of highly active antiretroviral therapy (HAART), with multiple medications, formulations, and dosing intervals, makes adherence challenging. Little is known about the adherence of children to HAART. The objective of this study was to identify correlates of adherence to HAART and the relationship between adherence and study outcomes in a pediatric clinical trial.

Methods. Pediatric AIDS Clinical Trials Group 377 is a phase I/II randomized trial of 4 HAART regimens in antiretroviral-experienced, clinically stable children aged 4 months to 17 years. The 4 treatment arms include various 3- or 4-drug combinations of d4T, 3TC, nevirapine, ritonavir, and nelfinavir. After informed consent was obtained, 193 children were enrolled between December 1997 and September 1998. Questionnaires were developed to collect subject- or caregiver-reported adherence to study medications and to identify problems associated with medication administration. Every 3 months, the number of doses of each medication missed during the 3 days preceding the study visit was recorded. Full adherence (FA) and non-full adherence were defined as missing no doses and missing at least 1 dose, respectively.

Results. Adherence data from study week 48 or the most recent study visit were available for 125 children (week 48 for 109 children). Overall, 70% of children reported FA and 30% reported non-full adherence. Adherence did not differ by treatment arm, age, or the child’s knowledge of his or her human immunodeficiency virus infection status. There was a suggestion that adherence was less for white than nonwhite children (40% vs 73% FA) and did not differ between black and Hispanic children. Rates of FA were 82% for d4T, 79% for 3TC, 83% for nevirapine, 84% for ritonavir, and 68% for nelfinavir. Despite the similar rates of FA, difficulties with taking specific medications were reported most frequently for ritonavir and nelfinavir. These included poor taste, patient refusal, and scheduling problems. Adherence was associated with the virologic response: FA was seen in 92% of children with ≥2 log10 drop in viral load and in 64% with <2 log10 drop in viral load.

Conclusion. In children, reported adherence predicts the virologic response to HAART therapy and is a useful measure of adherence. Interventions and regimens to increase adherence to HAART should result in an improved outcome. Pediatrics 2002;109(4). URL: http://www.pediatrics.org/cgi/content/full/109/4/e61; adherence, compliance, HIV, antiretroviral therapy, protease inhibitors.

ABBREVIATIONS. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; PACTG, Pediatric AIDS Clinical Trials Group; RT, reverse transcriptase; BID, twice-daily; TID, 3 times a day; FA, full adherence; NFA, non-full adherence.

Highly active combination antiretroviral therapy (HAART) is effective in suppressing human immunodeficiency virus (HIV) replication, preventing opportunistic infections, reducing mortality, and improving the well-being of children and adults with HIV infection. Inadequate suppression of viral replication by HAART can result from several problems, including 1) low potency of the antiviral regimen, 2) viral resistance, 3) inadequate drug exposure, and 4) poor adherence to therapy. Furthermore, incomplete suppression of viral replication in the presence of antiretroviral drugs can select for resistant strains of virus. HAART is unforgiving of lapses in therapy, with rates of adherence as high as 95% required to suppress viral replication maximally. Failure of HAART early in therapy is frequently attributable to poor adherence rather than to the development of resistant virus. Thus, in the evaluation of the efficacy of antiretroviral therapy, it is important to be able to measure adherence.

In adults, self-reported adherence is a good predictor of the virologic response to HAART. Little is known about the impact of adherence on the response to therapy in children with HIV infection, and measures of adherence have not been widely applied to antiretroviral therapy trials in children.
Factors that reduce adherence to combination HAART regimens in children include lack of a liquid formulation for some drugs, the large volume of medications often required, and the extremely poor palatability of some medications. A simple quantitative measure of adherence would be valuable in the evaluation of HAART in children.

Pediatric AIDS Clinical Trials Group (PACTG) Protocol 377 was undertaken to evaluate several promising HAART regimens consisting of various combinations of nucleoside reverse transcriptase (RT) inhibitors, protease inhibitors, and a nonnucleoside RT inhibitor. The major objectives of the study were to evaluate the degree of viral suppression, safety, and tolerance of the different regimens. A substudy was included to evaluate the pharmacokinetics, safety, and virologic response to twice-daily (BID) nelfinavir dosing (as opposed to 3-times-a-day [TID] dosing), a schedule that may increase patient adherence. Two Pediatric Adherence Questionnaire Modules were used to capture information regarding adherence to study treatments, including the number of missed doses of each medication during the preceding 3 days and difficulties associated with taking each medication. In adults, the number of missed doses during the preceding 3 days by self-report correlates well with the number of missed doses as measured by pill count and electronic medication monitoring.

METHODS

Study Design and Patients

PACTG 377 was a multicenter, randomized clinical trial that compared change from current therapy to 1 of 4 drug regimens, each of which contained BID stavudine (d4T): 1) d4T, BID nevirapine, and BID ritonavir; 2) d4T, BID lamivudine (3TC), and TID nelfinavir; 3) d4T, nevirapine, and nelfinavir; and 4) d4T, 3TC, nevirapine, and nelfinavir. Furthermore, 12 additional children who weighed 30 kg or less at study entry were enrolled in a fifth treatment arm of d4T, 3TC, and nelfinavir, in which the nelfinavir was administered BID rather than TID as in the other arms. All children had HIV infection, were aged 4 months to 17 years, had stable CD4 cell number or percentage maintained in Centers for Disease Control and Prevention Immune Category 1 or 2 during the 4 months before study entry, and were receiving continuous antiretroviral therapy for the 16 weeks before study entry. All were naive to d4T, 3TC, protease inhibitors, and nonnucleoside RT inhibitors. Exclusion criteria included current grade 3 or 4 toxicity (as judged by protocol-specified, standard pediatric toxicity criteria), active opportunistic or serious bacterial infection, and current diagnosis of malignancy or pregnancy.

Initially, PACTG 377 was not designed to investigate study treatment adherence. Two adherence questionnaires (PACTG Adherence Module 1 and 2) were added to the ongoing study when >60% of the children who had reached study week 12. PACTG Adherence Module 1 collects information on the ability of the child or caregiver to identify the antiretroviral medications and records the number of doses of each medication that were reported to have been missed during the preceding 3 days. Adherence Module 2 collects information on difficulties encountered with the administration of each medication. (PACTG Adherence Modules are available at www.stfrtr.org/qol/peds/pedadhere.html.) The adherence modules were administered in a standardized manner through use of a scripted dialogue. They were administered to the child when he or she was primarily responsible for taking his or her own medications. Otherwise, they were administered to the primary caregiver. The objectives of this adherence analysis were to validate the modules as a useful practical measure of adherence, to investigate the reasons for nonadherence, to determine whether adherence was uniform among the treatment arms, and to evaluate the association between adherence and clinical and laboratory outcomes.

The duration of study treatment for each child was initially planned to be 48 weeks but was extended to 96 weeks for children who were still on their initial treatment regimens. The institutional review board at each institution approved the study, and written informed consent, including agreement with the adherence evaluations, was obtained from all patients and their parents or legal guardians.

Study Evaluations

Both PACTG adherence modules were administered every 12 weeks beginning at study week 12 by a trained study nurse through an interview using a standardized scripted dialogue. They were administered to the child when he or she was primarily responsible for taking his or her own study medications; otherwise, they were administered to the caregiver who was principally responsible for administering the medications. Other study evaluations were performed within 14 days before randomization (the pre-entry visit), at study entry, and at follow-up visits that were conducted every 4 weeks while on study. These included a medical history, physical examination, and a complete blood count with differential and serum chemistries. Lymphocyte surface markers were evaluated at pre-entry; entry; study weeks 4, 8, 12, 16, and 24; and every 12 weeks thereafter and were performed by local laboratories participating in the National Institute of Allergy and Infectious Diseases Flow Cytometry Quality Assurance Program. Specimens for quantitative HIV-1 RNA were obtained at pre-entry; entry; study weeks 4, 8, 12, 16, 12, 12, 24, 36, 44, and 48; and every 12 weeks thereafter. HIV-1 RNA copy number was assessed using the Roche Amplicor Monitor Assay (Roche Diagnostics Corp, Indianapolis, IN) by a single laboratory at Johns Hopkins University (Baltimore, MD), which was certified as proficient for this assay by the National Institute of Allergy and Infectious Diseases Virology Quality Assurance Program. The lower limit of assay quantification for RNA was 400 copies/mL.

All adverse events were graded using protocol-specified, standard toxicity criteria for pediatric populations. Only those toxicity events that occurred during therapy or <60 days after termination of initial study medication were included in the analysis. Included in the present analysis are the data from the first 48 weeks of study treatment or until treatment discontinuation if this occurred before study week 48.

Statistical Analysis

The primary endpoint of this analysis was the adherence information obtained at the evaluable visit, defined as the week 48 study visit if available or at the latest visit before week 48. Adherence for a given patient at the evaluable visit was defined as full adherence (FA) when no doses of any study drugs were missed in the last 3 days before the visit. Non-full adherence (NFA) was defined as missing at least 1 dose of a study drug in the 3 days before the visit.

The baseline RNA value was defined as the geometric mean of the pre-entry and the entry RNA values. The baseline CD4 cell count and percentage and baseline weight were defined as the arithmetic mean of the pre-entry and entry values. The current RNA value, CD4 cell count/percentage, and toxicity grade were those obtained at the evaluable visit.

An intent-to-treat philosophy was used for this analysis; patients were analyzed according to their randomization assignment regardless of premature treatment discontinuation.

RESULTS

Baseline Patient Characteristics

A total of 193 children were enrolled into PACTG 377, 125 of whom (65%) had adherence information available and are included in this analysis. Of these
125 children, the evaluable visit was the week 48 visit for 109 (87%) and the week 24 or 36 visit for the remaining 16 (13%). At the evaluable visit, the source of the adherence information was a biological parent for 27% of children, an adoptive parent for 19%, a foster parent for 19%, the child him- or herself for 12%, and another primary caregiver for 23%. Twenty-nine percent of the children were aware of their HIV infection. The median age at entry was 6.3 years, the median baseline CD4 cell count was 655 cells/mm³, the median baseline CD4 percentage was 29%, and the median baseline plasma HIV RNA concentration was 22 400 copies/mL (Table 1). The 4 treatment groups had similar baseline characteristics (Table 1).

Adherence Among Treatment Groups

At the evaluable visit, the overall rate of FA was 70% (88 of 125; Table 2). Twenty-five percent (31 of 125) of children reported having missed some doses, and 5% (6 of 125) reported having missed all doses of all drugs in the preceding 3 days; these 2 groups were combined as the NFA group. The rates of FA for the different treatment regimens is shown in Table 2. All 7 children on the BID nelfinavir treatment regimen (group 5) reported FA (no missed doses of any drugs). Children who received d4T/nevirapine/ritonavir (group 1) had the highest rate of FA among the 4 main treatment groups (groups 1–4), whereas children who received the 4-drug combination regimen (group 3) had the lowest rate. However, there were no statistically significant pairwise differences with respect to the FA rate among these 4 groups. The FA rate was not significantly different between the ritonavir-containing treatment regimen (group 1) and the 3 TID-nelfinavir-containing treatment regimens (groups 2–4; 84% [21 of 25] vs 65% [60 of 93]; P = .09); there also was not a significant difference between the 3-drug combination treatment regimens (groups 1, 2, 4, and 5) and the 4-drug combination treatment regimen (group 3; 74% [69 of 93] vs 59% [19 of 32]; P = .12). There was a suggestion that the rate of FA was better for the BID nelfinavir-containing regimen (group 5; 100%) than for its corresponding TID nelfinavir-containing regimen (group 4; 63%; P = .08; Table 2).

The rate of FA for each individual drug was 82% (103 of 125) for d4T, 79% (56 of 71) for 3TC, 83% (71 of 86) for nevirapine, 84% (21 of 25) for ritonavir, and 68% (68 of 100) for nelfinavir. For children who received both d4T and nelfinavir (groups 2, 3, and 4), the rate of FA for TID-administered nelfinavir was significantly lower than for BID-administered d4T (66% vs 80%; P = .048). There were no significant pairwise differences between treatment groups with respect to the FA rate for each individual drug.

Association of Adherence With Baseline Factors

There was no significant association between treatment adherence and any of the following baseline characteristics: age at entry, weight, race/ethnicity, gender, the child’s knowledge of his or her HIV infection status, the nature of the person providing the adherence information (child, parent, caregiver), previous antiretroviral experience, sites from which patients were enrolled, plasma HIV RNA concentration, and CD4 cell count and percentage. There was a suggestion that white race was associated with poorer treatment adherence than nonwhite race (FA rate 40% [4 of 10] vs 73% [84 of 115]; P = .06). Adherence did not differ between black and Hispanic children.

Association of Adherence With Treatment Response

The reported adherence to study treatment was significantly associated with 2 measures of the virologic response to therapy: the HIV-1 plasma RNA level at the evaluable visit and the change in plasma RNA from baseline (Table 3). At the evaluable visit, children with an RNA level <400 copies/mL (the lower limit of detection) had a rate of FA of 77% (58 of 75) compared with 63% (10 of 16) for children with an RNA level between 400 and 800 copies/mL and 55% (17 of 31) for children with an RNA level >800 copies/mL (P = .02). At each study visit, the proportion of children with undetectable plasma HIV RNA was lower for those who reported NFA at that visit than for those who reported FA (Fig 1). These differ-

<p>| TABLE 1. Baseline Characteristics of Analyzable Children by Treatment Group |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>d4T/NVP RTV</th>
<th>d4T/NVP NFV</th>
<th>d4T/3TC NVP NFV</th>
<th>d4T/3TC NFV</th>
<th>d4T/3TC NFV (BID)</th>
<th>Overall</th>
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<tr>
<td>Number of patients (N)</td>
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<td>29</td>
<td>32</td>
<td>32</td>
<td>7</td>
<td>125</td>
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<tr>
<td>Median age (y)</td>
<td>5.1</td>
<td>5.3</td>
<td>6.6</td>
<td>7.2</td>
<td>7.4</td>
<td>6.3</td>
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<tr>
<td>Female gender (%)</td>
<td>52%</td>
<td>59%</td>
<td>53%</td>
<td>50%</td>
<td>71%</td>
<td>54%</td>
</tr>
<tr>
<td>Race or ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>64%</td>
<td>79%</td>
<td>50%</td>
<td>72%</td>
<td>100%</td>
<td>68%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>32%</td>
<td>17%</td>
<td>34%</td>
<td>19%</td>
<td>0%</td>
<td>24%</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
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<td>3%</td>
<td>16%</td>
<td>9%</td>
<td>0%</td>
<td>8%</td>
</tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>ddI</td>
<td>33%</td>
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<td>45%</td>
<td>38%</td>
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<td>41%</td>
</tr>
<tr>
<td>ZDV + ddI</td>
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<td>48%</td>
<td>48%</td>
<td>59%</td>
<td>57%</td>
<td>54%</td>
</tr>
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<td>Other</td>
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<td>6%</td>
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<td>Median CD4 cell count (cells/μL)</td>
<td>778</td>
<td>548</td>
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<tr>
<td>Median % CD4</td>
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<td>27%</td>
<td>32%</td>
<td>35%</td>
<td>29%</td>
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<tr>
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<td>20.4</td>
<td>21.9</td>
<td>34.7</td>
<td>24.0</td>
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d4T indicates stavudine; 3TC, lamivudine; NVP, nevirapine; RTV, ritonavir; NFV, nelfinavir; ddI, didanosine; ZDV, zidovudine.
enforcement approached significance at weeks 24 and 48. At week 48, undetectable RNA was present in 64% (55 of 86) of children with FA and 44% (16 of 36) with NFA (P = .07). FA was reported by 92% (22 of 24) of children with ≥2 log_{10} drop in viral load from baseline to the evaluable visit and by 64% (63 of 98) with <2 log_{10} drop in viral load (P = .01).

Adherence was significantly associated with 2 additional factors at the evaluable visit: the identity of the individual who responded to the adherence questionnaire and the formulation of the protease inhibitor (Table 3). The FA rate was 47% (7 of 15) when the child responded, 65% (22 of 34) when a biological parent responded, and 78% (59 of 76) when others responded (P = .04). Eighty-eight percent (22 of 25) of children who took a protease inhibitor in a liquid formulation reported FA, in contrast to 65% (62 of 96) of children who took a solid formulation (P = .03). There was no significant association between adherence and other factors at the evaluable visit, including age, CD4 cell count and percentage, children’s knowledge of their own HIV status, and the worst degree of drug toxicity.

**Reasons for Nonadherence**

Nonadherence was identified as a frequent problem or almost always a problem by 16% (20 of 122) of children who received d4T, 13% (9 of 70) who received 3TC, 19% (16 of 84) who received nevirapine, 44% (11 of 25) who received ritonavir, and 36% (35 of 98) who received nelfinavir. Difficulty with adherence was more commonly reported for the protease inhibitors than for the RT inhibitors. The main reasons stated for nonadherence were taste (16%) and child refuses (16%) for ritonavir and taste (9%) and scheduling/interferes with lifestyle (10%) for nelfinavir. Of the 23 children who specified that a problem existed for d4T, 3TC, and nevirapine, no single problem was reported by 10% or more.

**DISCUSSION**

We report an association between adherence and the virologic response to combination antiretroviral therapy in children with HIV infection, with a significantly greater reduction in plasma HIV concentration seen in children who reported FA. At 12 weeks of therapy, the proportion of children with full viral suppression (viral load <400 copies/mL) was similar in the groups that reported FA and NFA at the evaluative visit (Fig 1). However, at the 24-week visit and beyond, a higher proportion of children with FA had full viral suppression, with the difference approaching significance at 48 weeks. This suggests that with potent combination antiretroviral therapy, suppression of viral replication can initially be achieved by most children. However, the maintenance of virologic suppression is more difficult, requiring excellent adherence to complex drug regimens over a prolonged period of time. It has been suggested that up to 95% of doses must be taken to obtain optimal results with antiretroviral therapy.\(^4,15\) Furthermore, ongoing viral replication in the face of antiretroviral therapy will select for drug-resistant virus, rendering these drugs ineffective in the future. Thus, adherence remains the major challenge to successful antiretroviral therapy.

We elected to collect self-reported adherence information through a structured interview using a standardized script to maximize uniformity of data from site to site. Self-reported adherence was easy to obtain in the course of routine study visits. The script was designed to be nonjudgmental and to emphasize the importance of collecting accurate information on adherence during the preceding 3 days. It has been suggested that self-reporting may overestimate adherence because of a desire of the subject and family to please the providers.\(^14\) In addition, self-report reflects only recent behavior—it is difficult to recall missed doses beyond 3 days. More objective measures of adherence that may overcome these limitations are available. These include pill counts and pharmacy refill data, electronic monitoring systems that document when medication bottles are opened, and blood drug levels.\(^4,15\) However, all have limi-
tions, including greater complexity and cost than self-reporting, and may not be readily available at all clinical sites. In addition, results obtained by self-report, pill counts, and electronic monitoring have been shown to be correlated. Many sites commented that the interviews served a useful educational purpose by initiating a discussion of issues relating to adherence and allowing the children to discuss problems with medications.

Studies in adults have demonstrated that self-reported adherence predicts the response to antiretroviral therapy. It has been suggested that the use of a computer to collect self-reported information on adherence will produce more accurate data because there is less pressure to please the provider. However, this technique is not practical for routine use in young children and requires expensive equipment and training.

Two recent studies reported an association between reported adherence and virologic response in children. In a survey administered at 3 sites that participated in the Pediatric Spectrum of Disease Project, 90 caregivers were interviewed with regard to their child’s adherence to medications. Seventeen percent reported having missed at least 1 dose in the preceding 24 hours. A viral load of <400 copies/mL was found in 50% of the children who reported no missed doses and in 24% with missed doses, results similar to ours. In a retrospective review of children who received HAART at a single clinic, adherence, based on pharmacy records, was associated with virologic response to therapy. Children who had at least 75% of their prescriptions filled had a significantly greater likelihood of having full viral suppression.

The overall rate of FA (not missing any doses in the preceding 3 days) in our study population was 70% at 48 weeks. Although there are no significant differences between the treatment groups, there is a trend toward poorer adherence in the groups with more complex regimens: the group that received 4 medications (group 3) and the group that received 3 doses of nelfinavir a day (group 4; Table 2). The rates of FA for the children who received 4 study drugs was lower than for those who received 3 drugs (59% vs 74%; P = .12). Similarly, the small group that received BID nelfinavir reported 100% FA, suggesting that BID dosing may improve adherence to this medication. The power of these and other subgroup comparisons is limited by small numbers and should be confirmed in a larger sample. However, they do suggest that adherence can be enhanced if regimens are simplified.

Reported adherence for the individual medications was remarkably similar, with the exception of nelfinavir, which had a lower reported adherence; this difference reaches significance when nelfinavir is compared with d4T. The rate of adherence for the ritonavir-containing regimen seems higher than for the nelfinavir-containing regimens (84% and 65% FA, respectively). Because ritonavir was administered BID and nelfinavir was administered TID (with the exception of group 5), it is possible that the simplified dosing schedule of ritonavir contributed.
to its better adherence. Problems encountered with individual medications were reported most frequently for ritonavir (44% of children) and nelfinavir (36%). This is not surprising considering the bad taste of the ritonavir liquid and the difficulty in administering the powder formulation of nelfinavir. Indeed, bad taste and child refusal were commonly reported for the protease inhibitors. In the face of this, it is surprising that adherence to ritonavir was similar to that of the RT inhibitors. It may be that the ease of administration of the liquid formulation of ritonavir and the BID dosing schedule compensates for its poor taste. The large volume and unusual texture of the nelfinavir powder is particularly challenging for parents to administer. For instance, at the dose of nelfinavir used in this study (55 mg/kg BID), an average 6-year-old is required to take 5 tablets or 25 scoops of nelfinavir powder, with food, twice a day.

There was no correlation between adherence and age, baseline HIV viral load, or duration of previous antiretroviral therapy. Despite a small number of white children, there was a suggestion of better adherence among children of nonwhite race, but this observation likely reflects a variety of associated socioeconomic factors. Several factors in addition to the virologic response to therapy were significantly associated with the rate of FA (Table 3). Adherence was lowest when the children provided the adherence information themselves and highest when it was provided by a primary caregiver who was not a biological parent. This finding is likely to be confounded by age, with older children more likely to provide their own information. It may be that a caregiver is more likely to exaggerate the degree of adherence, whereas the children tend to be more honest about their own adherence. Conversely, these results may be true, suggesting that a concerned caregiver is more successful at administering medications than the children themselves. For instance, adherence to medications is a particular problem during adolescence. The formulation of the protease inhibitor also predicted adherence, with a liquid formulation being associated with better adherence. However, only ritonavir was available as a liquid formulation; nelfinavir is formulated as a powder for administration to children. Obviously a liquid formulation facilitates administration of medications to infants and young children. This emphasizes the importance of having liquid formulations available for all antiretroviral drugs. Currently among approved antiretroviral drugs, zalcitabine, delavirdine, efavirenz, indinavir, saquinavir, and nelfinavir are not available as liquid formulations.

CONCLUSION

Self-reported adherence, when collected in a standardized manner, is a useful measure of medication-taking behavior that predicts the virologic response to therapy. Although treatment failure may be attributable to viral resistance or inadequate drug exposure, it is often attributable to poor adherence. Thus, a simple means of assessing adherence by all patients during the course of treatment is essential to be able to identify and address problems early in the course of therapy. Interventions and regimens that improve adherence to HAART should result in an improved outcome. In the context of a clinical trial, it is important to be able to assess accurately what role adherence plays in the response to different treatment regimens. The measurement of adherence is complex, with multiple measures likely to give the most reliable results. However, self-reported adherence is simple and reliable and should be obtained from all children who receive antiretroviral therapy.

APPENDIX

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7 of 7
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