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Adherence to Antiretroviral Therapy for Pediatric HIV Infection: A Qualitative Systematic Review With Recommendations for Research and Clinical Management

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Abstract

Although nonadherence to prescribed therapies is widespread, it is particularly problematic with highly active antiretroviral therapy for HIV infection. This review of >50 studies in the area of pediatric HIV infection revealed varying methods for assessing antiretroviral adherence with a wide range of estimates of adherence. Correlates of adherence could be grouped as those relating to the medication, the patient, and the caregiver/family, with many conflicting findings and a lack of theory guiding the research. Only 8 studies, mainly small feasibility or pilot investigations, evaluated highly active antiretroviral therapy adherence interventions in pediatric populations. We conclude with specific recommendations for assessment and clinical management of adherence and discuss directions for future research in this area.

Keywords

HIV/AIDS; adherence; compliance; interventions; pediatric

Adherence to therapy, or the extent to which a patient's behaviors coincide with medical advice mutually negotiated between the health professional and the patient, is a universal

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challenge with all illnesses and in all age groups.¹ Each year in the United States, 500 000 physicians write 1.8 billion prescriptions involving 55 000 pharmacies.² However, many of these prescribed medications are never taken, with rates of nonadherence ranging from 15% to 93%.³ Among persons with chronic illnesses, nonadherence is especially problematic, occurring in up to 82% of cases.^{4–6} The effects of nonadherence range from individual disability (eg, unrelieved pain) to global threat (eg, development of treatment-resistant bacteria or viruses). The yearly monetary costs of nonadherence exceed \$100 billion.⁷

Adherence is particularly critical with highly active antiretroviral therapy (HAART) in the treatment of pediatric HIV infection. The data on HAART for pediatric HIV infection, although scarcer than for adults, suggest that medication adherence is a strong predictor of therapeutic impact.^{8,9} For example, Wiener et al¹⁰ observed that among children with an HIV-1 RNA viral load (VL) < 10 000, 75% had taken 100% of their medication doses in the previous week, whereas among those with a VL of ≥ 10 000, only 36% reported taking all of their medication.

Despite the benefits of HAART in treating pediatric HIV infection^{11–15} and the adverse consequences of nonadherence, adherence is reportedly suboptimal among children.^{16–20} It is likely thwarted by multiple barriers^{21,22} and complicated because, unlike with many other chronic illnesses, most children who are born with HIV in the United States are ethnic/racial minorities who live in chronic poverty with limited resources and face discrimination, family disruption, substance abuse, and the stressors of life in the inner city.²³ In addition, stigma is greater for HIV/AIDS than other chronic illnesses, which often leads caregivers to conceal the child's diagnosis and treatment from others and from the child as well. The energy spent on maintaining this secrecy can strain the family considerably. The practical barriers and psychological burden further complicate the administration of medications, which itself often serves as a painful reminder of the disease.²⁴

The global epidemic of HIV continues, with an increasing impact on children. By the end of 2004, an estimated 2.2 million children under 15 years of age worldwide were living with HIV; in that year alone, 640 000 were newly infected.²⁵ Although recent meta-analyses suggest that efforts to improve adherence to antiretroviral therapy among adults can be effective,^{26,27} much work remains to be done with children.

In an effort to guide clinicians and researchers with respect to pediatric HAART adherence, we conducted a qualitative systematic review of the research literature. We present (1) estimates of adherence and examine how they vary according to assessment method, (2) correlates of adherence (including barriers to adherence and reasons for nonadherence), and (3) strategies to improve adherence, with particular attention to those that have been evaluated empirically.

METHODS

A thorough and systematic search for published journal articles, abstracts, books, and ongoing studies on pediatric adherence to antiretroviral therapy was conducted via PubMed, PsycINFO, Medline, AIDSLINE, and the Computer Retrieval of Information on Scientific

Projects, an online database of ongoing federally funded biomedical research projects. We searched each database for work from January 1996 to December 2005 that included the 3 terms “HIV/AIDS,” “pediatric,” and “compliance/adherence” (equivalents for these terms also were used in the searches). In addition, we examined the reference lists of relevant articles and solicited information from colleagues. A team of 3 reviewers narrowed down the ~350 citations identified in the search to the ~50 that we cite in this review, mainly on the basis of their offering original data on the topic. We conducted a qualitative review of this literature and summarized nonnumerically the major findings.

RESULTS

Estimates of Adherence According to Assessment Method

As shown in Table 1, we found 32 studies that reported data that estimated antiretroviral adherence among pediatric populations. They were published between 1999 and 2005, with 69% of the studies based in the United States. Sample sizes ranged from 10 to 262 (median = 46), and participants were from 3 months to 24 years of age. Most participants were infected perinatally, but behaviorally infected individuals and those infected by contaminated blood products also were included in some studies.

The authors used most of the known methods for capturing antiretroviral medication adherence, including both direct and indirect methods. Direct methods such as biological assays of an active drug, its metabolite, or other markers in the bodily fluids confirm active drug ingestion. Indirect methods, which do not measure the presence of the drug in the individual, include self-report; caregiver report; clinician assessment; medical chart review; clinic attendance; pill count; pharmacy refill records; electronic drug monitoring (EDM); behavioral observation in the form of directly observed therapy (DOT) (sometimes during hospitalization); resistance testing; and therapeutic impact such as VL, CD4 lymphocyte count, Centers for Disease Control and Prevention–defined stage of disease progression, and mortality. Combinations of these methods to produce one adherence estimate also were used.

Notably, evidence for drug resistance, increasing VL, and decreasing CD4 lymphocyte count are commonly considered signs of nonadherence, but they are not well represented as assessment strategies in research studies of pediatric HAART adherence. In particular, VL is often assessed clinically, but in the research literature it is most commonly used to corroborate adherence reports or as an indicator of treatment success rather than as an estimate of adherence itself.

Caregiver and patient reports were the sole or main source of adherence data for most reports. Few studies used purportedly more-objective methods such as pill counts and EDM. Some studies used more than 1 method to collect adherence data but reported just 1 overall adherence estimate; this was done in 3 studies in which older children provided self-report data while caregivers provided data for the younger children and infants.^{13,28,29} Other studies combined self-report with clinical attendance data⁹ or provider reports with pill counts.³⁰

Adherence estimates varied greatly, precluding a meaningful summary of the extent of nonadherence. As seen in Table 1, results from the 13 studies that used caregiver reports indicated that 34% to 100% of caregivers reported 100% adherence, and 84% to 89% reported 95% adherence; reports of mean adherence according to caregivers ranged from 88.4% to 96%. Self-reports, which were used in 8 studies overall, indicated that 20% to 58% of patients reported 100% adherence, 44% reported 95% adherence, and 58% to 70% reported 90% adherence; self-reported mean adherence ranged from 93% to 97%. In the 5 studies with pharmacy refill data, assessment intervals ranged broadly (from 90 to 365 days), and widely different definitions of adherence were used (eg, 75% filled, 90% filled, median filled). Thus, it is difficult to provide a single summary estimate of adherence on the basis of pharmacy refill data. For example, 1 study reported that 100% of prescriptions were refilled,³¹ and another reported that only 58% of participants filled >75% of their prescriptions.³² Fairly high adherence was estimated by the 2 studies by using pill counts (in which mean adherence was ~87%) and in the 3 studies using care providers (in which adherence averaged 82%–100%). In the 3 studies that assessed adherence by clinic attendance, estimates varied almost linearly according to the assessment interval, with lower levels for longer intervals. For example, perfect clinic attendance was achieved by 21% of the patients in the previous 365 days,³³ 65% in the previous 180 days,³⁴ and 88% of patients in the previous 90 days.^{31,33} As seen in Table 1, the 3 studies that used therapeutic drug monitoring, the 2 that relied on medical chart review, and the 2 with EDM generally produced lower estimates of adherence than did studies using the other methods.

The range in estimates of adherence may reflect the heterogeneity of the samples. For example, age varied widely both within and across samples, and medication-taking among 4-month-olds is obviously a very different phenomenon than among adolescents. Another possible reason for the variation is that study participants were on varying antiretroviral regimens, and adherence can differ according to medication as a result of variations in such factors as palatability or tolerability.³⁵ For example, in 1 study, full adherence varied from a low of 59% to a high of 100% depending on the regimen.²⁹

Differences in study methodology also may have contributed to the wide range of adherence estimates. How adherence was assessed (eg, pill counts or self-report); how optimal adherence was defined (eg, cut points of 90%, 95%, or 100%); and how findings were reported in each study (eg, as a range, a median percentage for the whole sample, or the percentage of participants who achieved a predetermined benchmark) varied considerably. Furthermore, some studies counted only doses taken on time as completed.¹⁰ Assessment intervals (when reported) varied from 1 day to 1 year and were associated with adherence at least as assessed by clinic attendance.

The studies that used multiple adherence-assessment strategies in the same sample (ie, triangulation) allowed for a more useful comparison of adherence estimates because the differences in samples were controlled. The 6 studies in our review that used multiple methods to capture adherence, which were all based in the United States, are described below.

With 5 separate methods, Farley et al³⁴ assessed adherence among 26 children aged 21 months to 12.5 years. Median adherence was found to be higher according to caregiver report (100%) and clinic attendance (100%) than pharmacy refill (92%) and EDM (81.4%). Data on provider assessment were not reported.

Among 42 patients aged 4 months to 18 years, Byrne et al³¹ used 4 methods of assessing adherence. They noted full adherence in the 7 days before assessment for 97% of the sample according to caregiver report (mean: 88.4%). Over 90 days, they noted full adherence for 88% according to clinic attendance and 100% according to pharmacy refill. Median adherence according to the providers was 82.5% (assessment interval was not reported).

Three other studies also concluded that caregivers generally overestimated adherence compared with other methods.^{36–38} With 73 children under the age of 13 years, Mellins et al³⁶ reported that full adherence in the 30 days before assessment was 60% according to caregiver report versus 44% according to self-report. In the Naar-King et al³⁷ sample of 40 children aged 2 to 17 years, mean adherence the day before the interview was 96% according to caregivers and 93% according to self-report. In 30 children under 12 years of age, Steele et al³⁸ found that caregiver reports of adherence in the 3 days before assessment averaged 94.3%; over the previous 90 days, adherence according to pill counts averaged 89.9% and that according to EDM averaged 44%.

Wiener et al¹⁰ used a multisite sample of 35 individuals aged 11 to 21 years to examine adherence with provider ratings, self-report interviews, and daily telephone diaries. They found that providers (ie, clinical nurses) reported uniformly high adherence (all but 1 estimated it was 90%). Over the week before the assessment, self-reported full adherence on the basis of doses taken on time (12%) was less than for doses taken at all (32%); both were less than the 44% adherence estimated based on daily telephone diaries that did not directly query about medication-taking.

Factors Related to Adherence

Researchers commonly investigate factors related to adherence as answers to questions such as: What are the challenges or barriers to adherence? What are reported reasons for nonadherence? Which variables predict nonadherence, or what might facilitate optimal adherence? Lists of factors presented are more likely to be derived from clinical experience or surveys in selected areas such as “mental health and coping”³⁹ than from theory-driven research or studies in which the associations were examined statistically.^{19,31,40–42}

Pontali⁴³ grouped factors that were capable of influencing adherence into those related to the medication, health care system, and patient and family/caregiver. They stressed the role of family disruption and the characteristics of the caregiver such as his or her relationship to the child, level of anxiety and depression, education, substance use, attitudes toward treatment, and his or her own HIV infection status.

Proposed medication or treatment-related factors that likely complicate pediatric adherence include the indefinite duration of treatment; multiple and precise dosing times; multiple medications; high pill burden; complex dietary considerations; storage requirements; low

palatability (ie, bitter-tasting liquids and gritty, sticky powders); large pills; significant short-term and long-term adverse effects (eg, nausea, rashes, hypersensitivity reactions, lipodystrophy, and anemia); and long-term toxicities.^{43,44} Studies have demonstrated better adherence with a twice-per-day (vs 3-times-per-day) nelfinavir regimen, shorter length of time since treatment initiation, and nelfinavir rather than indinavir but not with pill burden or drug toxicity.^{18,29,35,36}

Pontali⁴³ cited such factors as the availability and cost of the medications, accessibility of treatment, and health care providers' experience and relationship to the patient as health care system variables that are possibly associated with adherence. We found no studies that specifically evaluated the association between such variables and pediatric antiretroviral adherence.

In pediatric disease, developmental challenges, especially during adolescence, are the major patient factors that complicate HAART adherence. Marhefka et al⁴¹ wrote that adolescents have the same difficulties as adults with fitting a complex regimen into their life, but they have less autonomy, privacy, and mobility than adults. A qualitative study of 6 HIV-infected teenagers aged 16 to 24 years in Rhode Island found that many of the major factors that negatively influenced adherence were the same as those in adults. These factors included fear of social stigma related to HIV disclosure, complexity of the regimen, adverse effects, forgetfulness, depression, absence of symptomatology, lack of general knowledge about HIV, and poor provider-patient relationship.⁴⁵ However, the authors observed other factors that were unique to the developmental stage of the teenagers: familial overinvolvement and the youth's focus on gaining rewards in the present versus planning for the future. Similarly, in a study of 29 HIV-positive French adolescents, participants reported that in addition to loneliness and depression, secrecy and silence about their HIV diagnosis and treatment were major barriers to their sense of freedom, with nonadherence becoming a way to express their need for autonomy. Given these challenges of adolescence, it is perhaps not surprising that adherence generally decreases as teenagers assume increasing responsibility for their medication-taking.⁴⁶

Other research on patient factors revealed findings that were often inconsistent. Some studies indicated that pediatric antiretroviral adherence was not related to gender, age, race, child's knowledge of HIV status, structural social support, satisfaction with social support, or health status/virologic or immunologic factors.^{18,19,29,36,39,47} Other studies indicated that patient factors associated with better adherence were nonwhite (versus white) race, both younger and older age of child, child's unawareness of his or her HIV diagnosis, beliefs regarding the positive impact of the medications on quality of life, lower intensity of alcohol use, housing stability, less depressive symptomatology and child stress, decreased child responsibility for medications, and improved health status/virologic or immunologic factors.^{17-19,28,29,36,39,47}

Family/caregiver factors are crucial to pediatric adherence, because infants and younger children depend almost entirely on a caregiver to administer medications. Their adherence to treatment, therefore, is largely determined by the resources and efficacy of their caregivers, who often struggle to administer medications to children who resist, refuse, or spit them out.

Caregivers who are biological parents of HIV-positive children often share their diagnosis and confront challenges associated with their own illness and its comorbidities. Thus, they may be physically fatigued or debilitated. In these cases, treatment can become a reminder of the parents' guilt about their role in their child's acquisition of infection, which is yet another challenge to adherence.⁴⁸

Research on family/caregiver variables has indicated that children are more adherent if they receive their medications from foster parents rather than biological parents or other relatives.^{29,47} Parents of adherent children report higher perceptions of their ability to administer the prescribed doses and of the medication efficacy and less concern about others discovering their child's diagnosis.^{16,48} The accuracy of caregivers' information about the child's HIV medications and corresponding dosages and dosing frequencies has been related to adherence, as has the number of barriers.^{33,41} In a study of 75 perinatally infected 3- to 13-year-olds in New York, Mellins et al³⁶ found that nonadherence was related to worse parent-child communication, higher caregiver stress, lower caregiver quality of life, and worse caregiver cognitive functioning. However, in a sample of 30 infants and children under 12 years of age, Steele et al³⁸ noted no association between adherence and parental perceived vulnerability or perceived barriers.

Overall, the literature on factors related to pediatric antiretroviral medication adherence (summarized in Table 2) has been largely atheoretical. Hammami et al,⁴⁹ however, presented findings that confirmed the information-motivation-behavioral skills model.⁵⁰ Specifically, in their qualitative study of 11 caregivers of HIV-positive children in Belgium, adherence was associated with (1) knowledge of the disease and its treatment; (2) motivation or willingness to adhere (which depended on the acceptance of the HIV diagnosis, the emotional quality of the mother-child relationship, and the recognition of future prospects); and (3) the capacity or ability to adhere (which depended on having the necessary cognitive and technical skills to follow a medication scheme, perceived self-efficacy, and problem-solving capacity).

Evaluations of Strategies to Improve HAART Adherence

Many studies of factors related to adherence also suggest strategies for improving HAART adherence, but few of these studies have been subject to empirical examination. We found 7 studies that focused on the evaluation of interventions to enhance antiretroviral medication adherence among pediatric populations, all of which were conducted in the United States. As described below, only 1 involved a randomized, control trial⁵¹; the other reports presented primarily descriptive data on small samples.⁵²⁻⁵⁷

Gigliotti et al⁵² studied a DOT intervention, primarily to determine if prolonged elevation of VL could be attributable to poor adherence. They identified 6 perinatally infected children aged 3.3 to 11.5 years with elevated VLs for periods of months to years and for whom suboptimal adherence was suspected. DOT was administered in the hospital for 4 children and at an HIV program-sponsored summer camp for the other 2 children. DOT of 4 to 8 days lowered the VLs of all 6 of these heavily drug-experienced children with advanced HIV, exceeding a 90% decrease (1.0 log₁₀) in 4 of them. Surprisingly, as few as 4 days of DOT resulted in a 70% (0.5 log₁₀) drop in VL.

Roberts et al⁵³ examined an intensive DOT program among 6 families of children who showed continued high VLs for several years despite documentation of viral sensitivity to the prescribed medication regimen and caregiver assertions of regular medication administration. Their stepwise approach involved an initial referral to a home health nurse and then DOT supplemented by intensive education and counseling provided for patients and caregivers during a 4-day hospitalization and at 2 weeks postdischarge, and, if necessary, a physician-initiated medical-neglect report to state authorities. Although 5 of the 6 families cooperated with the visiting nurses, the referrals failed to result in sustained improvements in adherence. This lack of success was attributed to the many logistic problems of in-home visits and the lack of specialized training of the nurses. Four of the 6 patients responded to DOT, with sustained decreases in VLs. Medical-neglect reports did not improve adherence in the 2 other children, who demonstrated improvements in VLs and immune functioning after subsequent placement in foster care.

Lyon et al⁵⁴ had 23 HIV-positive black youths aged 15 to 23 years and 23 family members or other “treatment buddies” participate in a 12-week educational program. Six meetings included family members, and 6 meetings were with the youths only; all meetings were 2 hours and included a meal. Devices such as watches, pill boxes, and calendars were introduced. Three months postintervention, 91% self-reported improved adherence. Care managers corroborated these reports. None of the youths had significant improvements in VL (defined a priori as a 1-log reduction in VL or undetectable VL); however, 4 participants demonstrated improved immune functioning.

Via a retrospective medical chart review, Shingadia et al⁵⁵ located 17 perinatally infected children who had gastrostomy tube (GT) insertion for improvement of medication adherence at the median age of 2.9 years (range: 1.25–11.8 years). In the year after the procedure, all 17 patients were noted to be “adherent” by care providers, although a clinically significant improvement (ie, 2-log reduction in VL) was found in only 10 cases. The authors attributed this discrepancy to the initiation of a new medication regimen at the time of the procedure for all 10 of these patients, who showed improvement over the next year. They recommended, therefore, that the HAART regimen be changed after GT placement to minimize the impact of viral resistance secondary to nonadherence. Despite the intrusiveness of the medical procedure to insert the tubes, they were reportedly well tolerated by the children. Caregivers noted satisfaction with the devices, reductions in medication administration time, and improvement in child behavior during medication administration.

Rogers et al⁵⁶ evaluated the only theory-driven intervention, which was based on Prochaska’s stages-of-change model.⁵⁸ It involved an intensive 8-week program with 13- to 22-year-olds using videotape and audiotape material appropriate to assess stage of readiness to adhere with HAART: precontemplation, contemplation, preparation, action/maintenance, and relapse. The material was designed primarily for treatment-naïve subjects to prepare them for successful initiation of HAART and long-term maintenance of adherence. Youths were to watch the videos with the study coordinators and then were offered the tapes to take home and share with family members. During the preparation program, participants practiced a regimen with surrogate pills for 1 to 2 weeks. Evaluation was hampered by high attrition (only 18 of the 65 enrollees completed the full program), which the authors

attributed to difficulties in scheduling program visits and the labor-intensive nature of the intervention. Among these 18 participants, 78% moved forward in terms of their stage of readiness, and two thirds accepted HAART, with half of them maintaining adherence “most to all of the time.”

Ellis et al⁵⁷ evaluated a clinical program that used home-based multisystemic family therapy delivered by mental health specialists, averaging 46 therapy sessions over 7 months. Children and families were referred to the program on the basis of their adherence problems or high VLs in the absence of resistance. Ninety percent accepted the referrals, and 95% received a full dose of treatment, which suggested high program feasibility. Among the 19 children aged 1 to 16 years who participated, caregiver-reported adherence did not change (likely because of ceiling effects according to the authors), but chart-abstracted VLs were found to significantly decrease from referral to the end of treatment. The mean change reflected a >1-log decrease in VL, and this change persisted through the 3-month follow-up as well.

In the only randomized, controlled trial, Berrien et al⁵¹ evaluated home nursing visits as a means of increasing adherence with 67 families. The home visits were designed to identify and resolve barriers to medication adherence, but specific barriers addressed by the intervention were not reported, with the exception of pill-swallowing training. In the treatment group, knowledge scores significantly improved, and self-reported adherence marginally improved.

In addition to these 7 published reports of study evaluations, we found 2 ongoing trials of adherence interventions, both of which were sponsored by the Centers for Disease Control and Prevention.

Pediatric Impact is a large multisite randomized, controlled trial of an intervention to improve adherence to antiretroviral therapy. It involves children aged 5 to 13 years and their primary caregivers in New York City and Washington, DC.⁵⁹ The intervention includes a dedicated adherence coordinator, an initial needs assessment, and tailored modular interventions, including home-based services. Enrolled children and their caregivers are randomly assigned to either a “minimal” or “enhanced” arm and offered an individualized combination of the following 6 modules: HIV education, HIV diagnosis-disclosure education to children, behavior modification, medication swallowing, medication management, and referrals to social and mental health services.

Adolescent Impact, a randomized, controlled trial of an intervention to improve adherence to treatment and reduce sexual transmission risk behavior in youth aged 13 to 21, is currently ongoing in New York City, Baltimore, Maryland, and Washington, DC, at 5 clinical sites.⁶⁰ The study includes adolescents with perinatally acquired infection and those who acquired their infection through sexual risk behavior. The intervention provides education, social support, and skills training through an integrated series of one-on-one and group sessions. Seven group sessions address health and developmental issues common to youth with HIV; 5 one-on-one sessions are used to tailor prevention messages to the unique health and risk

profile of each teen. To aid adherence, participants receive organizational tools including a personal digital assistant with adherence software; an optional home visit is also provided.

DISCUSSION

In this qualitative systematic review of the literature on medication adherence in pediatric HIV, we located over 50 relevant studies, although many were purely descriptive and the empirical studies often included small samples. Researchers used a range of strategies for measuring adherence, with patient self-report or caregiver reports being the most common. In contrast to previous reports of suboptimal adherence, we found that estimates of adherence varied widely. Heterogeneous samples and methods complicated comparisons of adherence estimates both within and across studies. Correlates of adherence were reported atheoretically, generally as variables related to the medication, patient, or caregiver. Overarching models for understanding correlates and predictors of adherence were noticeably lacking, as were investigations of the role of societal and health care system factors. The literature on the development and formal evaluation of theory-driven strategies for improving adherence remains sparse. Overall, this review of the available literature leaves unanswered many key questions regarding adherence to antiretroviral medication in pediatric HIV infection.

Recommendations for Assessing Adherence

The literature across adult and childhood illness suggests each adherence-assessment method has advantages and disadvantages, with the trade-off generally assumed to be financial and logistic cost versus psychometric and epidemiologic accuracy.^{61–64} Reports from the patient, caregiver, or provider are the least expensive and most widely used methods, but they tend to overestimate adherence compared with other methods. Caregivers and patients are prone to social desirability and recall bias, and providers often misjudge adherence. However, 2 recent reviews demonstrated the validity of self-reports from adult patients, at least in terms of their associations with VL.^{65,66} Although EDM is often considered the gold standard and can provide useful data on timing and patterns of missed doses, it is subject to nonuse, and its high cost makes it impractical in most settings.⁶⁷ Pharmacy refill data are clouded by the practice of some pharmacies to automatically mail medications at prescribed periods. Clinical variables such as VL are affected by numerous other factors such as the innate variability of disease activity and presence of resistant strains of virus.

Assessing adherence in pediatric populations poses specific challenges.^{13,64,68} The direct methods such as measurement of blood levels of medications are expensive, and the lack of information on the pharmacokinetics and pharmacodynamics of pediatric formulations of HAART medications renders interpretation of such data difficult.^{69,70} Even when relevant data are available, individual variations in metabolism and developmental changes complicate the task. In addition, the presence of measurable levels of a drug only means that the child took the last dose of that medication. Many pediatric formulations of HAART medications are available only in powder/liquid form, which restricts the utility of EDM and pill counts (although remaining powder and liquid medication can be quantified). Putting the

liquid/power bottle within an EDM bottle has not been shown to be feasible.³⁴ Prepackaged pill boxes or syringes further limit the use of EDM. Self-reports among children are subject to their cognitive abilities and developmental level. Caregiver report is subject to the vantage point of the individual making the report. Most children are cared for by many different caregivers. The parent or guardian, other family member, baby-sitter, home health aide, and school nurse each have different yet probably incomplete information about the specifics of medication-taking. No one individual is consistently the most reliable. For example, younger children may completely depend on a caregiver and know nothing about their prescribed regimens, whereas caregivers of older children play a much more peripheral role, perhaps just occasionally reminding the child to take a dose or administer a small percentage of doses.

The data from studies of pediatric HAART adherence fail to provide definitive guidelines or to identify any gold standard in terms of assessment methods. However, the limitations of any single assessment strategy suggest possible benefits of using multiple methods (or triangulation). Although methods other than self-report may be too unreliable (provider estimates), burdensome (telephone diaries), or costly (EDM) to use routinely in clinical settings, they might be considered for short-term use or to illuminate issues with respect to clinical care. Clinicians should remember that VL, which is often used as the criterion with which to compare adherence-assessment methods, is not a perfect indicator of adherence, especially in heavily and sequentially treated perinatally HIV-infected adolescents, in whom resistance occurs frequently.¹⁰

Face-to-face interviews can be administered quickly and easily and offer maximum flexibility in terms of asking about different classes of medications and times and amount of each dose.¹⁰ Simple inquiries about whether the child took the morning dose of the medication and then tracing backward to the evening and the day before can be followed by how many doses could not be given in the previous week. This or a simple question about how many doses were missed in the previous week may be an appropriate starting point.^{10,27,66,71} Questions regarding difficulties in administering medications such as child resistance or lack of disclosure of diagnosis to a temporary caregiver are useful as well. Providers should also elicit information regarding baby-sitting arrangements and methods used by the caregivers to remind others of the need for medication-taking.

A comprehensive assessment of adherence cannot be accomplished in 1 meeting but ideally is part of a structured program of adherence monitoring, allowing clinicians to identify nonadherence early and to focus on the families who have the most difficulty. Wiener et al¹⁰ advised assessing adherence during every visit and determining if nonadherence is confined to a particular drug or exists across medications. Reports of nonadherence provide opportunities to address problems and barriers. Dolezal et al¹³ suggested interviewing both the child and the caregiver, perhaps followed by a joint interview to reconcile any discrepant reports. Sensitivity to patients' culture is key, according to DeRouen and Jackson,⁷² who recommended that providers examine their own personal biases; assess the patient's background and cultural identification, including views of life, spirituality, death and dying, and the value of outside support systems; and be accepting, nonjudgmental, and flexible. Questions should facilitate reports of nonadherence (eg, "I understand it is very difficult to

administer these medications to children; have you been able to give any to your child this week?”) rather than incriminating (eg, “We have talked about how important good adherence is. You have not missed any doses lately have you?”). Statements regarding how difficult it is to give all doses of medications in a timely fashion and maintenance of a nonjudgmental attitude throughout the interview are crucial. Assessing reasons for nonadherence (eg, work schedule, caretaking responsibilities for other family members, attempts to avoid thinking about the illness, caregiver’s own ill health) and patterns of nonadherence (eg, always missing the morning dose, missing doses on the weekends) is key to determining the appropriate intervention. It is important to remember that adherence to HAART is a dynamic and lifelong process. Crises, a new job, caregiver illness, a new relationship, a different baby-sitter, loss of housing, and a multitude of other factors that affect families can wreak havoc on medication administration in even the most adherent family.

Recommendations for Improving Adherence

Our review of the empirical literature on the efficacy of HAART-adherence interventions for pediatric populations located only 7 published studies, of which only 1 was a randomized, controlled trial. These studies provided some support for the utility and efficacy of DOT, a 12-week educational program, GT placement, and nursing home visits. However, most findings were based on pilot studies with very small samples, and adherence to the intervention itself was often problematic. The findings suggest that more intensive interventions are required to produce efficacious outcomes and that 1-time interventions in the absence of ongoing education and support may be insufficient. Overall, they exemplify the barriers that are often encountered in this challenging work. Although clinicians commonly assume that certain medications or regimens are easier to tolerate than others or rely on drug holidays to reinvigorate adherence efforts, the literature is sparse and inconsistent regarding the treatment-related factors that affect adherence. Many of these interventions have become clinical lore and require additional scrutiny.

With a few exceptions, much of the literature on strategies for enhancing adherence relies on clinical-practice wisdom.^{43,68} On the basis of work with adolescents and young adults, Dodds et al⁷³ cited the benefits of adopting a developmental framework, fostering buddy systems, and determining psychological and psychosocial treatment readiness. They stressed the need for intensive, continuous, coordinated, and nurturing case management services, with screening and treatment for mental health problems and substance abuse. Program components that are important for adherence, in their experience, include colocation of key services, home visits, transportation, child care at home or in the facility, incentives, and reminder telephone calls and letters. In a review of the literature, Pontali et al⁷⁴ noted the following patient and family strategies: setting up an adherence program, intensive education in preparation for HAART initiation (perhaps even hospitalization), use of reminders such as diaries and alarms, disclosure, inclusion of older children in the decision-making process, and DOT and GT insertion if necessary.

Given the lack of definitive work on medication-adherence strategies in pediatric HIV infection, clinicians might seek guidance from the research in other pediatric chronic illnesses, which share many of the challenges of HIV infection.^{63,64} Studies in the area of

pediatric tuberculosis suggest that DOT may be a viable strategy, although there are important differences between treatments for the 2 diseases.⁷⁵ Among children with asthma, juvenile rheumatoid arthritis, and type 1 diabetes, myriad adherence-intervention strategies have been examined.⁷⁶ Educational strategies focus on providing written and verbal information to patients and their families about the illness and the regimen requirements, as well as the importance of adherence and anticipatory coping strategies for potential adverse effects. Organizational strategies emphasize simplifying regimens and changing clinic characteristics such as improving supervision of providers, decreasing waiting times, and boosting accessibility. Behavioral strategies incorporate visual reminders such as medication calendars and self-monitoring into the child's daily schedule. They comprise encouraging parental support, dispensing incentives for desirable behaviors, and offering clinical interventions for the treatment of underlying behavioral and emotional difficulties in the patient and family. A review of the literature in these diseases revealed that "probably efficacious" strategies include organizational interventions, multicomponent packages, and operant learning and that behavioral, educational, and cognitive-behavioral strategies are "promising."⁷⁶

Recommendations for Future Research

Future research should focus on evaluating the validity and reliability of self-report adherence measures, because they are the most widely used and most practical tools for assessing adherence in clinic settings. Comparison between self-report and more objective measures and clinical indicators are needed to identify the most cost-effective assessment strategies.¹⁰ In addition, more data on the pharmacokinetics and pharmacodynamics of pediatric formulations of HAART medications will make therapeutic drug monitoring a more reliable method of assessment.

To investigate adherence levels and potential correlates of adherence, future research should incorporate prospective studies, perhaps beginning at HAART initiation and continuing throughout the disease course both in domestic and international settings. Steele and Grauer²⁰ advised systematically examining factors that may predict adherence and developing risk profiles to target potential nonadherers. We need additional examination of factors related to caregivers (such as cognitive variables) and psychosocial adjustment and stress.^{16,38} Work is needed on the development and evaluation of theoretical models that incorporate multiple domains of influence, especially contextual factors. Models that have been applied successfully to HAART adherence among adult samples include those that are based on theories of stress and coping,⁷⁷ social support,⁷⁸ self-efficacy,⁷⁹ and social problem-solving⁸⁰; these may be worth investigating among pediatric samples. Qualitative data may facilitate the application of theoretical models to the complex context of pediatric HIV infection. For example, interventions will need to consider the normative developmental tasks faced by children with HIV infection as they survive into adolescence, including separation from adult figures and achieving a sense of mastery or control, which may incur risk-taking behavior that jeopardizes self-care with chronic illness. Theories that emphasize self-efficacy and social problem-solving are likely to be particularly relevant to adolescent developmental concerns and may be especially engaging if presented through high-technology modes such as the Internet.^{81,82}

This research agenda will require multisite studies and the incorporation of non-US-based sites to increase sample size. The most efficacious interventions will likely need to go beyond merely cognitive intervention and education and counseling and will be long-term.^{45,68} Standardization of assessment methods and definitions of adherence in future work will facilitate the comparison of research results.

Critically important is the need to expand work in international settings and resource-constrained environments, where the pediatric HIV epidemic is expanding exponentially and the need for improved strategies for addressing adherence is most dire. Many developing countries have no health care infrastructure and no models for the management of chronic diseases. The increased access to antiretroviral therapy in these areas needs to be coupled with strategies to address adherence. Research in the area of biomedical strategies may be especially relevant for clinical care in areas in which personnel to assist with adherence are scarce. Although empirical data are limited for many of these options, future work should investigate the effect of more palatable formulations, possibly liquids that do not require refrigeration or small-sized pills that need be taken less frequently. More tolerable formulations, with fewer adverse effects, toxicities, and dietary requirements, also might be helpful.⁴³ There is urgent need to develop innovative medication-delivery systems such as skin patches for antiretroviral therapy. These biomedical interventions may need to be combined with patient-focused educational and behavioral strategies and then reinforced by attention to larger structural issues such as access to care and decreasing stigma to effectively confront the challenges of pediatric HIV treatment.

CONCLUSIONS

Nonadherence to antiretroviral therapy has catastrophic consequences. Much work remains to be done to develop a meaningful multisystemic and effective yet cost-effective approach to assess and improve adherence to antiretroviral therapy for children with HIV infection.

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Abbreviations

HAART	highly active antiretroviral therapy
VL	HIV-1 RNA viral load
DOT	directly observed therapy
EDM	electronic drug monitoring
GT	gastrostomy tube

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TABLE 1
Estimates of Pediatric Antiretroviral Adherence According to Assessment Method

Results	Assessment Interval, d		Study Description			
	N	Age	Route of Infection	Location	Ref No.	
Caregiver report of 100% adherence, %						
adherent						
100	3	26	21 mo to 12.5 y	IP	Baltimore, MD	34
97	7	42	4 mo to 18 y	NR	New York, NY	31
83	1	90	15 mo to 14 y	NR	Boston, MA	16
79.5	3	44	1 to 17 y	IP	Genova, Italy	74
76	3	37	8 y (median)	IP	Genova, Italy	40
74	7	262	3 mo to 16 y	NR	Europe and Brazil	44
73	3	11	4 mo to 19 y	NR	Belgium	49
68.2	30–60					74
67	21	18	4 to 15.5 y	IP	Sydney, Australia	83
60	30	75	3 to 13 y	IP	New York, NY	36
57	7					16
34	NR	34	18 mo to 20 y	NR	South Carolina	33
Caregiver report of 95% adherence, %						
adherent						
89	21					83
84	4	129	4 mo to 17 y	NR	Multisite, Italy	47
Caregiver report, mean adherence, %						
96	1	40	2 to 17 y	IP	Detroit, MI, and New York, NY	37
94.3	3	30	0.9 to 11.5 y	NR	Memphis, TN	38
88.4	NR					31
Self-report of 100%, % adherent						
58	1	42	16 to 24 y	NR	Chicago, IL	84
44	30					36
41	NR	161	12 to 19 y	IB	Multisite, US	19
34	7					84
32.4	7	35	11 to 21 y	40% IP; 60% BP	Multisite, US	10

Results	Assessment Interval, d	Study Description			Ref No.
		N	Age	Route of Infection	Location
20	14				
Self-report of 95% adherence, % adherent					
44	14				
Self-report of 90% adherence, % adherent					
70	NR	88	13 to 22 y	NR	NR
69.8	30	231	15 to 22 y	IB	Multisite, US
61	90	31	13 to 24 y	80% IB, 13% BP	Los Angeles, CA
58	1				
Self-report, mean adherence, %					
97	30				
93	1				
Pharmacy refill					
100% filled	90				
92% adherent (median)	180				
22% to 100% adherent	365				
49% to 90% adherent	90	51	2 to 12 y	IP	Jacksonville, FL, and Baltimore, MD
58% filled 75%	180	72	3 mo to 12 y	IP	Baltimore, MD
Pill count					
"Most" had 85%	30	80	NR	NR	Cape Town, South Africa
89.9% adherent (mean)	90				
Care provider report					
82.5% adherent (mean)	NR				
82% adherent (mean)	30				
97% reported 100% adherence	NR				
Clinic attendance					
88% kept 100%	90				
65% kept 100%	180				
21% kept 100%	365				
Therapeutic drug monitoring, % adherent					
66	50	3.8 to 16.8 y	NR		PACTG cohort, US

Results	Assessment Interval, d	Study Description			Ref No.
		N	Age	Route of Infection	
50		10	4 to 170 mo	IP	87
54–100		40	3 mo to 18 y	NR	35
Medical chart review, % adherent					
54		NR	NR	69 IP; 1 BP	8
28		NR	13 to 21 y	17 IB; 1 BP	18
EDM					
81.4% (median)		180			34
44% (mean)		90			38
Self-report and caregiver report of 100% adherence (combined), % adherent					
70		3	4 mo to 17 y	NR	29
67		30	4.3 to 13 y	IP	28
54 ^a		2	7.3 to 13.7 y	IP	13
Self-report and clinic attendance (combined)					
27% “good”		168	8 to 22 y	IB	9
Pharmacy refill and pill count (combined)					
19% to 95% were “adherent”		NR	3 mo to 15 y	IP	30
70% (mean)					

NR indicates not reported in the original article; IP, infected perinatally; IB, infected behaviorally; BP, infected by blood products; PACTG, Pediatric AIDS Clinical Trials Group.

^aIn 54% of all patient/caregivers dyads, both reported 100% adherence.

TABLE 2

Research on Factors Related to Pediatric Antiretroviral Adherence (Based on Quantitative Research With Tests of Statistical Significance)

Significantly Associated With Adherence	Nonsignificantly Associated With Adherence
Medication related	
Twice-per-day (vs 3-times-per-day) nelfinavir regimen; shorter length of time since treatment initiation; nelfinavir rather than indinavir	Pill burden; drug toxicity
Patient related	
Nonwhite (vs white) race; both younger and older age of child; children's unawareness of their HIV diagnosis; beliefs regarding the positive impact of the medications on quality of life; lower intensity of alcohol use; housing stability; less depressive symptomatology; less child stress; decreased child responsibility for medications; improved health status/virologic or immunologic factors	Gender; age; race; child's knowledge of HIV status; structural social support; satisfaction with social support; health status (virologic or immunologic factors)
Caregiver/family related	
Foster (vs biological) parent; higher self-efficacy; belief in the efficacy of the medication; less concern about hiding child's diagnosis; better parent-child communication; less caregiver stress; higher quality of life; better caregiver cognitive functioning; better caregiver knowledge of antiretroviral medications; fewer barriers	Parental perceived vulnerability; perceived barriers