



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again before changing regimens (**AIII**).
- Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence (**AIII**).
- At least one method of measuring adherence to ART (such as quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load (**AII**).
- When feasible, once-daily antiretroviral regimens should be prescribed (**AI***).
- To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care (**AII***).

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

Background

Adherence is a **determinant of viral suppression and fundamental to successful antiretroviral therapy (ART)**.¹⁻⁴ Prospective adult and pediatric studies have shown **a direct correlation between** risk of virologic failure and proportion of missed doses of **antiretroviral (ARV)** drugs.⁵ Based on early work in populations of adults primarily being treated with nonboosted protease inhibitor (PI)-based regimens,² 95% adherence has been the threshold associated with complete viral suppression. Recent findings from adult populations suggest that the relationship between ARV adherence and viral suppression may vary with individual drug, drug class, and pattern of adherence.⁶ Viral suppression can be achieved with lower levels of adherence when using boosted PI and non-nucleoside reverse transcriptase inhibitor regimens.^{6,7} In patients who achieve suppression, the longer the duration of suppression the lower the level of adherence necessary to prevent viral rebound.⁸ Different patterns of inadequate adherence (intermittent missed doses, treatment interruptions) may have a differential impact on regimen efficacy, depending on the drug combination.^{9,10}

Subtherapeutic ARV drug levels resulting from poor adherence may facilitate development of drug resistance to one or more drugs in a given regimen, and possibly cross-resistance to other drugs in the same class. Multiple factors (including regimen potency, pharmacokinetics, viral fitness, and the genetic barrier to ARV resistance) influence the adherence-resistance relationship.¹¹ In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens in patients who develop drug-resistant viral strains **and in transmission of HIV to sexual partners**.

Evidence indicates that adherence problems are common in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to prescribed regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), ARV regimens, and study characteristics.^{3, 4, 12-14} A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial and behavioral characteristics of children and parents, have been associated with adherence; however, no clear predictors of either good or poor adherence in children have been consistently identified.^{12, 15-19} Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.²⁰ These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence education, support, and assessment integral components of care.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient and family factors, and characteristics of health care providers.¹⁷ Limited availability of palatable formulations for young children is especially problematic.^{5, 21} Furthermore, infants and children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments, as well as the ability and willingness of a child to take the drug. Barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal.^{22, 23} Some caregivers may place too much responsibility for managing medications on older children before the children are developmentally able to take on such tasks,²⁴ whereas others may face health and adherence challenges related to HIV infection or other medical conditions. Many other barriers to adherence exist for HIV-infected children. For example, caregivers' unwillingness to disclose a child's HIV infection status to the child and to others may create specific problems, including reluctance of caregivers to fill prescriptions locally, hiding or relabeling of medications to maintain secrecy within the household, avoidance of social support, and a tendency for doses to be missed if the parent is unavailable. Furthermore, adherence also may be jeopardized by social issues within a family, such as illicit substance abuse, unstable housing, and involvement with the criminal justice system.

Specific Adherence Issues in Adolescents

HIV-infected adolescents also face specific adherence challenges.^{25, 26} Several studies have identified pill burden as well as lifestyle issues (that is, not having medications on hand when away from home, change in schedule) as barriers to complete adherence.^{15, 27} Denial and fear of their HIV infection is common in adolescents, especially youth who have been recently diagnosed; this may lead to refusal to initiate or continue ART. Distrust of the medical establishment, misinformation about HIV, and lack of knowledge about the availability and effectiveness of ARV treatments all can be barriers to linking adolescents to care and maintaining successful ART. Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they may have long histories of inadequate adherence. Regimen fatigue also has been identified as a barrier to adherence in adolescents.²⁸ Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness because of lack of familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease all correlate with nonadherence.^{25, 29} In a study of 833 HIV-infected Medicaid beneficiaries aged 12 to 17 years, youth diagnosed with a psychiatric comorbidity (substance abuse, conduct disorder, or emotional disorder) were less likely to be receiving combination therapy; however, for those on therapy, only a conduct disorder diagnosis was associated with poorer adherence.³⁰ In a cross-sectional study of youth perinatally infected with HIV, no significant differences in the frequency of mental health disorders were found between adherent and nonadherent participants.³¹ A review of published papers on adherence among HIV-infected youth, however, suggests that

depression and anxiety have been consistently associated with poorer adherence.²⁹ Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties face adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and adolescents who are homeless and have no place to store medicine. When recommending treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ARV regimen with realistic assessment of existing and potential support systems to facilitate adherence.

Interventions to promote long-term adherence to ART have not been rigorously evaluated in adolescents. In clinical practice, reminder systems, such as beepers, **cellphones**, and alarm devices, are well accepted by some youth. Small, inconspicuous pillboxes may be useful for storing medications in an organized fashion. In a pilot study evaluating peer support and pager messaging in an adult population, peer support was associated with greater self-reported adherence post-intervention; however, the effect was not sustained at follow-up. Although pager messaging was not associated with reported adherence, improved biologic outcomes were measured.³² Another study evaluating the efficacy of a 4-session, individual, clinic-based motivational interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months in youth taking ART. However, reduction in viral load was not maintained at 9 months.³³

Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom ART initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by children and their families and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership with a child and family regarding medication management. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain a patient's explicit agreement with the treatment plan, including strategies to support adherence. Also, it is important to alert patients to minor side effects of ARV drugs, such as nausea, headaches, and abdominal discomfort that may recede over time or respond to change in diet or method and timing of medication administration.

Adherence is difficult to assess accurately; different methods of assessment have yielded different results, and each approach has limitations.^{14, 34, 35} Both caregivers and health care providers often overestimate adherence. Use of multiple methods to assess adherence is recommended.^{35, 36} Viral load response to a new regimen is often the most accurate indication of adherence, but it may be a less valuable measure in children with long treatment histories and multidrug-resistant virus. Other measures include quantitative self report of missed doses by caregivers and children or adolescents (focusing on recent missed doses during a 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Caregivers may report number of doses taken more accurately than doses missed.³⁷ Also, targeted questions about stress, pill burden, and daily routine are recommended.^{38, 39} Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports.⁴⁰ Electronic monitoring devices, such as Medication Event Monitoring System caps, which are equipped with a computer chip that records each opening of a medication bottle, have been shown to be useful tools to measure adherence in some settings.⁴¹⁻⁴³ **Mobile phone technologies, such as interactive voice response and text messaging, are being evaluated to quantify missed doses and provide real-time feedback on adherence to caregivers, but studies in the pediatric population are in the pilot phase.**⁴⁴ Home visits can play an important role in assessing adherence. In some cases, suspected nonadherence is confirmed only when dramatic clinical responses to

ART occur during hospitalizations or in other supervised settings. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring, may be a useful method to identify nonadherence⁴⁵ and drug concentrations in hair are now being studied as an alternative method to measure adherence.^{46, 47}

It is important for clinicians to recognize that nonadherence is a common problem and that it can be difficult for patients to share information about missed doses or difficulties adhering to treatment. Furthermore, adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A nonjudgmental attitude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both the HIV-infected children and their caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources.⁴⁸

Strategies to Improve and Support Adherence

Intensive follow-up is required, particularly during the critical first few months after therapy is started. Patients should be seen frequently, as often as weekly during the first month of treatment, to assess adherence and determine the need for strategies to improve and support adherence. Strategies include development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (such as associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers—rather than one specific intervention—may be most effective.^{24, 49, 50} Programs designed for administration of directly observed combination therapy to adults in either the clinic or at home have demonstrated successful results in both the United States and in international, resource-poor settings.⁵¹⁻⁵³ Modified directly observed therapy (m-DOT), where one dose is administered in a supervised setting and the remaining doses are self-administered, appears to be both feasible and acceptable.^{49, 54} However, a recent meta-analysis of 10 randomized clinical trials evaluating DOT to promote adherence in adults found that it was no more effective than self-administered treatment.⁵⁵ In another meta-analysis of DOT studies, DOT was found to have a demonstrated effect on virologic, immunologic, and adherence outcomes, but efficacy of the strategy was not supported when the analysis was restricted to randomized controlled trials.⁵⁶ [Table 16](#) summarizes some of the strategies that can be used to support and improve adherence to ARV medications.

Regimen-Related Strategies

ARV regimens often require administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects.⁵⁷ When nonadherence is a problem, addressing medication-related issues, such as side effects, may result in improvement. If a regimen is overly complex, it can be simplified. For example, when the burden of pills is great, one or more drugs can be changed to result in a regimen containing fewer pills and potentially greater adherence. When feasible, once-daily regimens should be prescribed. Several studies in adults have demonstrated better adherence with once-daily versus twice-daily ARV regimens.⁵⁸⁻⁶¹ When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can be masked with a small amount of flavoring syrup or food (see [Appendix A: Pediatric Antiretroviral Drug Information](#)) or a child can be taught to swallow pills in order to overcome medication aversion.⁶²

Child/Family-Related Strategies

The primary approach taken by the clinical team to promote medication adherence in children is patient and caregiver education. Educating families about adherence should begin before ARV medications are initiated or changed and should include a discussion of the goals of therapy, the reasons for making adherence a priority, and the specific plans for supporting and maintaining a child's medication adherence. Caregivers should understand that the first ARV regimen has the best chance of long-term success. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

A number of behavioral tools can be used to integrate taking medications into an HIV-infected child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives for taking medications, can be effective tools to promote adherence.^{63, 64} Training children to swallow pills has been associated with improved adherence at 6 months post-training in a small study of children aged 4 to 21 years.⁶⁵ Availability of mental health services and treatment of mental health disorders also may facilitate adherence to complex ARV regimens. A gastrostomy tube can be considered for nonadherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications.⁶⁶ If adequate resources are available, home nursing interventions also may be beneficial.⁶⁷ Directly observed dosing of ARV medications has been implemented in adults, adolescents, and children, using home nursing services as well as daily medication administration in the clinic setting. Other strategies to support adherence that have been employed in the clinical setting include setting patients' cell phone alarms to go off at medication times; providing pill boxes and other adherence support tools; weekly filling of pill boxes by nursing or pharmacy staff, particularly for patients with complex regimens; and home delivery of medications. Two recent studies conducted in adults in Kenya found that individuals who received cell phone text messages had significantly improved ART adherence. In one study, ART-naïve adults initiating treatment received weekly short message service (SMS) from a clinic nurse and were required to respond.⁶⁸ Self-reported adherence and rates of HIV-1 viral suppression at 12 months were significantly greater in individuals randomized to SMS compared with standard-of-care adherence support. Similarly, in second study, adult participants who received weekly SMS reminders were more likely to achieve high levels of adherence and less likely to experience treatment interruptions.⁶⁹

Health Care Provider-Related Strategies

Providers have the ability to improve adherence through their relationships with families. This process begins early in a provider's relationship with a family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important.^{70, 71} Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child-centered and includes caregivers in adherence support also has been shown to improve treatment outcomes.⁷²

Table 16. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care.
• Obtain explicit agreement on need for treatment and adherence.
• Identify depression, low self-esteem, substance abuse, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat mental health issues before starting antiretroviral (ARV) drugs, if possible.
• Identify family, friends, health team members, or others who can support adherence.
• Educate patient and family about the critical role of adherence in therapy outcome.
• Specify the adherence target: $\geq 95\%$ of prescribed doses.
• Educate patient and family about the relationship between partial adherence and resistance.
• Educate patient and family about resistance and constraint of later choices of ARV drug (that is, explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent).
• Develop a treatment plan that the patient and family understand and to which they feel committed.
• Establish readiness to take medication by practice sessions or other means.
• Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency and number of pills.
• Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities.
• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).
• Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects.
• Simplify food requirements for medication administration.
• Prescribe drugs carefully to avoid adverse drug-drug interactions.
• Assess pill-swallowing capacity and offer pill-swallowing training.
Follow-up Intervention Strategies
• Monitor adherence at each visit and in between visits by telephone or letter as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties associated with demands to attain 95% adherence with medication doses.
• Use patient education aids including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, alarms, pagers, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.
• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
• Provide pharmacist-based adherence support, such as medication education and counseling, refill reminders, and home delivery of medications.
• Consider gastrostomy tube use in selected circumstances.
• Consider directly observed therapy (DOT) at home, in the clinic, or during a brief inpatient hospitalization.

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