Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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 assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence (AIII).
- In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used (AIII).
- Once-daily antiretroviral regimens and regimens with low pill burden should be prescribed whenever feasible (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/adolescents, but not studies limited to post-pubertal adolescents

Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression. Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, as well as subtherapeutic or partial dosing.1,2 Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of drug resistance to one or more drugs in a given regimen and possible cross-resistance to other drugs in the same class. Multiple factors (including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance) influence the adherence-resistance relationship.3 In addition to compromising the efficacy of the current regimen, suboptimal adherence can limit the options for future effective drug regimens in patients who develop multidrug-resistant HIV and increase the risk of secondary transmission of drug-resistant virus.

Poor adherence to ARV drugs is commonly encountered in the treatment of children and adolescents living with HIV. A variety of factors—including medication formulation, frequency of dosing, drug toxicities and side effects, child’s age and developmental stage, as well as psychosocial, behavioral, and sociodemographic characteristics of children and caregivers—have been associated with nonadherence. However, no consistent predictors of either good or poor adherence in children have been identified.4,6 Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.7 These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work with patients and their families to ensure that adherence education, support, and assessment are integral components of care.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by the drug regimen, patient and family factors, and the patient-provider relationship.8,9 The limited availability of once-daily and single-tablet regimens and palatable formulations for infants and young children is especially problematic.10 Furthermore, infants and children are dependent on others for medication administration; barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal.11,12 Some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.13 Adherence may also be jeopardized by social and health issues within a family (e.g., substance abuse, poor physical or mental health,
Adherence Assessment and Monitoring

Clinicians should begin assessing potential barriers to adherence and discussing the importance of adherence with patients before therapy is initiated or changed. A comprehensive assessment should be instituted for all children with HIV before initiating or changing an ART regimen. Evaluations should assess social and behavioral factors that may influence adherence by children and their families and should identify individual needs for intervention. Clinicians should ask patients about their experience with taking medications, 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. It is also important to alert patients to potential adverse effects of ARV drugs (e.g., nausea, headaches, abdominal discomfort, sleep disturbances), explain how they can be managed, and emphasize the importance of informing the clinical team if they occur.

A routine adherence assessment should be incorporated into every clinic visit. Adherence is difficult to assess accurately; different methods of assessment have yielded different results and each approach has limitations. Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals on ART (see Plasma HIV-1 RNA [Viral Load] and CD4 Count Monitoring in the Adult and Adolescent Antiretroviral Guidelines). In addition, it can be used as positive reinforcement to encourage continued adherence. Clinicians should use at least one other method to assess adherence in addition to monitoring viral load. Table 13 includes commonly employed approaches to monitoring medication adherence.

Strategies to Improve and Support Adherence

If there are concerns about adherence, a patient should be seen and/or contacted frequently (by phone, text messaging, email, and social networking, as allowed within the context of local legal and regulatory requirements) to assess adherence and to determine the need for strategies that can improve and support adherence. During the first month of treatment, a patient can be contacted weekly, or even daily, if necessary.

Strategies should include simplifying the drug regimen, developing treatment plans that integrate medication administration into daily routines (e.g., associating medication administration with daily activities such as brushing teeth), and optimizing the 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 may be more effective than one specific intervention. The evidence is mixed as to the efficacy of programs that are designed to improve adherence by administering directly observed therapy (DOT), but DOT may still be a useful strategy for some patients. Table 14 summarizes some of the strategies that can be used to support and improve adherence to ARV medications. The Centers for Disease Control and Prevention (CDC) offers a web-based toolkit (consisting of four evidence-based HIV medication adherence strategies) to HIV care providers.

Regimen-Related Strategies

ARV drug regimens for children often require taking multiple pills or unpalatable liquids, each with potential adverse effects (AEs) 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 the number of daily doses, and chosen to minimize drug interactions and AEs. Efforts should be made to reduce the pill burden and pill size and to prescribe once-daily ARV drug regimens and single-tablet regimens whenever feasible (see Table 16 in Management of Children Receiving Antiretroviral Therapy). With the introduction of new drug classes and a wider array of once-daily formulations, including some medications that are now available in a small pill size, there are now more options to offer less toxic, simplified regimens, particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-
daily ARV drug regimens than with twice-daily ARV drug regimens, and better adherence with single-tablet formulations than with multiple-tablet regimens.\textsuperscript{10,31,32} Appendix A, Table 1 shows which ARV drugs are available in fixed-dose combination (FDC) tablets, and Appendix A, Table 2 provides information about minimum body weight requirements and other considerations when using FDCs in children.

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 sometimes be masked with a small amount of flavoring syrup or food (see Appendix A: Pediatric Antiretroviral Drug Information).\textsuperscript{33} Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children aged 4 years to 21 years found that training children to swallow pills has been associated with improved adherence at 6 months post-training.\textsuperscript{34} Finally, if drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs by changing the particular drug (or, if necessary, drug regimen) when feasible.

**Patient/Family-Related Strategies**

The primary approach 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 importance of optimizing adherence, and the specific plans for supporting and maintaining a child’s medication adherence. 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. Additionally, it may be helpful to assess the medication adherence of the caregiver or other household members who are known to be taking ARV drugs or other chronic medications.

Several behavioral tools can be used to integrate taking medications into a child’s daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives (including financial incentives) for taking medications, can be effective tools to promote adherence.\textsuperscript{35} Availability of mental health services and the treatment of mental health disorders (such as depression) may facilitate adherence to complex ARV drug regimens.\textsuperscript{36,37}

In situations where the child has not been informed of their HIV status, HIV disclosure should be discussed with the caregivers. In a recent review that explored the relationship between ART adherence and disclosure, five studies linked disclosure to improved adherence, four studies found that disclosure led to worse adherence among study participants, and five studies found no association.\textsuperscript{38} Therefore, the decision to disclose HIV status should not necessarily be expected to improve adherence. The decision should instead be based on a comprehensive assessment of the psychosocial milieu and the needs of the child and family.

In poorly adherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications, a gastrostomy tube may be considered.\textsuperscript{39} If adequate resources are available, home-nursing interventions or DOT may also be beneficial.

Other strategies to support adherence include mobile applications (apps) that remind patients to take medications; setting patients’ cell phone alarms to go off at medication times; sending text-message reminders; conducting motivational interviews; providing pill boxes, blister packaging, and other adherence support tools; and delivering medications to the home. The CDC has an adherence toolbox, which includes a free mobile app (CDC’s Every Dose Every Day mobile app) that is available through their website. Several randomized clinical trials in adults have demonstrated an association between text-message reminders and improved adherence.\textsuperscript{40-44} However, a recent randomized clinical trial in Uganda that involved adolescents and young adults found no difference in electronically measured adherence between participants who received text-message reminders about adherence and those who received standard adherence support.\textsuperscript{45} On the other hand, a small study in poorly adherent adolescents and young adults with HIV in the United States demonstrated that two-way personalized daily text messaging improved self-reported adherence.\textsuperscript{46} It should
be noted, however, that the evidence base for effective adherence interventions in adolescents and young adults who are taking daily ART is limited.47-51

Health Care Provider-Related Strategies
To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients and caregivers, and identify mutually acceptable goals for care. Providers can improve adherence through their relationships with patients’ 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. Provider characteristics that have been associated with improved patient adherence in adults include consistency, willingness to give information and ask 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. Immigrant children and families may face unique social and cultural issues; it is important to recognize these issues and facilitate establishing links to community resources, particularly for families who are recent immigrants. Providing comprehensive multidisciplinary care (e.g., with nurses, case managers, pharmacists, social workers, psychiatric care providers) may also better serve more complex patient and family needs, including adherence.

Table 13. Evidence-Based Approaches for Monitoring Medication Adherence

<table>
<thead>
<tr>
<th>Routine Assessment of Medication Adherence in Clinical Care</th>
<th>Description</th>
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<tbody>
<tr>
<td>Monitor viral load.</td>
<td>Viral load monitoring should be done more frequently after initiating or changing medications.a</td>
</tr>
<tr>
<td>Assess quantitative self-report of missed doses.</td>
<td>Ask the patient and/or caregiver about the number of missed doses over a defined period (1, 3, or 7 days).</td>
</tr>
<tr>
<td>Elicit description of medication regimen.</td>
<td>Ask the patient and/or caregiver about the name, appearance, and number of medications, and how often the medications are taken.</td>
</tr>
<tr>
<td>Assess barriers to medication administration.</td>
<td>Engage the patient and caregiver in a dialogue about facilitators and challenges to adherence.</td>
</tr>
<tr>
<td>Monitor pharmacy refills.</td>
<td>Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.</td>
</tr>
<tr>
<td>Conduct announced and unannounced pill counts.</td>
<td>Approaches include asking patients to bring medications to the clinic, home visits, or referral to community health nursing.</td>
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</table>

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<tr>
<th>Targeted Approaches to Monitoring Adherence in Special Circumstances</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement DOT.</td>
<td>Include brief hospitalization if indicated.</td>
</tr>
<tr>
<td>Measure plasma drug concentration.</td>
<td>Measuring plasma drug concentrations can be considered for particular drugs.</td>
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<tr>
<th>Approaches to Monitoring Medication Adherence in Research Settings</th>
<th>Description</th>
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<tbody>
<tr>
<td>Measure drug concentrations in hair.</td>
<td>This is a good measure of adherence over time.19,52,53</td>
</tr>
<tr>
<td>Use electronic monitoring devices.</td>
<td>These include MEMS caps and Wisepill.</td>
</tr>
<tr>
<td>Use cell phone-based technologies.</td>
<td>These include interactive voice response, text messaging, and mobile apps.</td>
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a See Clinical and Laboratory Monitoring of Pediatric HIV Infection regarding the frequency of adherence assessment after initiating or changing therapy.

Key to Acronyms: apps = applications; DOT = directly observed therapy; MEMS = Medication Event Monitoring System
Table 14. Strategies to Improve Adherence to Antiretroviral Medications

**Initial Intervention Strategies**

- Establish trust and identify mutually acceptable goals for care.
- Obtain explicit agreement on the need for treatment and adherence.
- Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or the caregiver that may affect adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.
- Identify family, friends, health team members, and others who can support adherence.
- Educate the patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and the potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.
- Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them to arrange for administration in day care, school, and other settings, when needed. Consider home delivery of medications.
- Establish a patient’s readiness to take medication by staging practice sessions or by other means.
- Schedule a home visit to review medications and determine how they will be administered in the home setting.
- In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess the tolerability of the chosen medications.

**Medication Strategies**

- Choose the simplest regimen possible, reducing dosing frequency, pill size, and number of pills (see Appendix A, Table 1 and Appendix A, Table 2).
- When choosing a regimen, consider the patient’s daily and weekly routines and potential 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 AEs; provide anticipatory guidance for management of AEs.
- Simplify food requirements for medication administration.
- Prescribe drugs carefully to avoid adverse drug-drug interactions.
- Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.

**Follow-up Intervention Strategies**

- Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.
- Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.
- Use patient education aids, including pictures, calendars, and stickers.
- Encourage use of pill boxes, reminders, mobile apps, alarms, 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, blister packs, refill reminders, automatic refills, and home delivery of medications.
- Consider DOT at home, in the clinic, or in certain circumstances, such as during a brief inpatient hospitalization.
- Consider gastrostomy tube use in certain circumstances.
- Information on other interventions to consider can be found at the Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions on the CDC’s website.
- Consult the CDC Every Dose Every Day toolkit.

Key to Acronyms: apps = applications; ARV = antiretroviral; AE = adverse effect; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy
References


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51. Camacho-Gonzalez AF, Gillespie SE, Thomas-Seaton L, et al. The Metropolitan Atlanta community adolescent rapid
