Each patient with an incomplete virologic response to therapy should be assessed to determine the cause of treatment failure because the approach to management and subsequent treatment may differ depending on the etiology of the problem. In most instances, treatment failure is multifactorial. Assessment of a child with suspicion of virologic treatment failure should include evaluation of adherence to therapy, medication intolerance, issues related to pharmacokinetics (PK) that could result in low drug levels or elevated, potentially toxic levels, and evaluation of suspected drug resistance. The main barrier to long-term maintenance of undetectable plasma viral load in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the antiretroviral (ARV) regimen.

Table 19 outlines a comprehensive approach to evaluating causes of virologic treatment failure in children, with particular attention to adherence. An extensive history should focus on the details of drug administration as well as changes in the social and psychological circumstances of the family likely to impact the child’s ability to adhere to therapy. In some situations, it may be necessary to directly observe drug-taking behaviors either in the clinic, at home, or in the hospital because history alone may not fully identify the barriers to complete adherence.1,2

**Adherence Problems** (For more details, see Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents and Table 11.)

When treatment failure is observed, clinicians need to assess the likely contribution of adherence problems to the failure of the current regimen. In patients on initial therapy, poor virologic response or widely fluctuating...
viral loads—particularly in the presence of susceptible virus—are commonly an indication of poor adherenc e. Depending on the specific drug regimen, even small lapses in adherence can lead to cART failure. Although adherence should be addressed at each medical visit for all children receiving cART, suspicion of treatment failure warrants increased scrutiny of adherence. Patterns of adherence can change over time and may be influenced by a large number of factors inherent to the drugs as well as social and psychological issues of children and their families.

It is important to evaluate whether adherence problems are related to drug formulation, number of pills, drug dose timing and frequency, food or fasting requirements, or drug side effects in order to determine changes best suited to the individual requirements of a child and his or her family. Family education concerning adherence should be intensive and include training in the administration of prescribed medications with emphasis on the importance of adherence to the drug regimen. Familial or social issues that impede adherence may need to be addressed before adherence can be improved. Issues to be addressed include financial or housing insecurity, concomitant mental health problems, need for substance abuse treatment, and fear of HIV disclosure. In some situations, clinicians may need to involve outside agencies, such as child protective services, to ensure support of a child’s treatment. Various interventions should be considered if problems within the household are extreme and unlikely to resolve in favor of successfully supporting a child’s treatment. Frequent patient visits and intensive follow-up may be necessary to support new adherence interventions and efforts by the child and the family to improve adherence to the current or new regimen. Directly observed therapy (DOT) may be used to identify additional factors impeding adherence as well as to confirm drug administration; however, durability of adherence improvement is variable after DOT is discontinued.  

**Pharmacokinetic Factors**

Treatment failure can result from inadequate drug exposure as well as poor adherence. Children consistently require higher weight-based dosing of ARV drugs than do adults because of developmental differences in absorption, body composition, and metabolic activity through the pediatric age range. Causes of subtherapeutic drug levels may include failure to increase dosing to accommodate for a child’s rapid growth or impaired absorption because of gastrointestinal symptoms such as vomiting or diarrhea. Because drug exposure can be enhanced or reduced by administering medications with food, a clinician should review the food/fasting requirements of a regimen with both patient and caregiver. Drug interactions can alter drug metabolism; therefore, all concomitant medications, including over-the-counter medications and nutritional and herbal supplements, should be reviewed to evaluate whether they may be contributing to poor treatment response (see the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). Several studies suggest that genetic polymorphisms may influence PK and therapeutic response for a number of antiretroviral (ARV) medications. In some circumstances, therapeutic drug monitoring can be considered for children receiving selected drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).

**Suspected Drug Resistance** (See Antiretroviral Drug-Resistance Testing)

ARV drug resistance may develop in children who are taking ARV drugs in the context of inadequate viral suppression. Genotypic resistance testing can help assess adherence to therapy. If testing reveals no resistance-associated mutations to the drugs in the current regimen, it is unlikely that the child is currently taking these medications. The presence of mutations that confer resistance to one or more drugs in the regimen is consistent with patient adherence (partial or full) to the regimen at that time, but failure of the regimen to adequately suppress viral replication because of drug resistance. Because virus variants harboring resistance mutations may decrease in frequency to below the limits of detection of standard resistance assays in the absence of the selective pressure of ARV drugs, ARV resistance testing should be performed while a patient is still taking the failing regimen or within 4 weeks of discontinuing the regimen. Resistance testing can be used to assess reasons for current virologic failure and to identify active ARV medications for future regimens. (See Antiretroviral Drug-Resistance Testing.)
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<tr>
<th>Cause of Virologic Treatment Failure</th>
<th>Assessment Method</th>
<th>Intervention</th>
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<tr>
<td>Non-Adherence</td>
<td>1. Interview child and caretaker&lt;br&gt;• Take 24-hour or 7-day recall&lt;br&gt;• Obtain description of:&lt;br&gt;  • WHO gives medications&lt;br&gt;  • WHEN medications are taken/given&lt;br&gt;  • WHAT medications are taken/given (names, doses)&lt;br&gt;  • WHERE medications are kept/administered&lt;br&gt;• Have open-ended discussion of experiences taking/giving medications and barriers/challenges&lt;br&gt;2. Review pharmacy records&lt;br&gt;• Assess timeliness of refills&lt;br&gt;3. Observe medication administration&lt;br&gt;• Observe dosing/administration in clinic&lt;br&gt;• Conduct home-based observation by visiting health professional&lt;br&gt;• Admit to hospital for trial of therapy&lt;br&gt;• Observe administration/tolerance&lt;br&gt;  • Monitor treatment response&lt;br&gt;4. Conduct psychosocial assessment&lt;br&gt;• Make a comprehensive family-focused assessment of factors likely to impact adherence with particular attention to recent changes:&lt;br&gt;  • Status of caregiver, housing, financial stability of household, child/caretaker relationships, school, and child’s achievement level&lt;br&gt;  • Substance abuse (child, caretaker, family members)&lt;br&gt;  • Mental health and behavior&lt;br&gt;  • Child/youth and caretaker beliefs about cART&lt;br&gt;  • Disclosure status (to child and others)</td>
<td>• Identify or re-engage family members to support/supervise adherence&lt;br&gt;• Establish fixed daily times and routines for medication administration&lt;br&gt;• To avoid any patient/caregiver confusion with drug names, explain that drug therapies have generic names and trade names, and many agents are co-formulated under a third or fourth name.&lt;br&gt;• Explore opportunities for facility or home-based DOT&lt;br&gt;• Simplify medication regimen, if feasible&lt;br&gt;• Substitute new agents if single ARV is poorly tolerated&lt;br&gt;• Consider gastric tube placement to facilitate adherence&lt;br&gt;• Consider DOT&lt;br&gt;• Use tools to simplify administration (e.g., pill boxes, reminders [including alarms], integrated medication packaging for AM or PM dosing)&lt;br&gt;• Suggest relaxation techniques&lt;br&gt;• Address competing needs through appropriate social services&lt;br&gt;• Address and treat concomitant mental illness and behavioral disorders&lt;br&gt;• Initiate disclosure discussions with family/child&lt;br&gt;• Consider need for child protective services and alternate care settings when necessary</td>
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Table 19. Assessment of Causes of Virologic Antiretroviral Treatment Failure (page 2 of 2)

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<tr>
<th>Cause of Virologic Treatment Failure</th>
<th>Assessment Method</th>
<th>Intervention</th>
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<tr>
<td>Pharmakinetik and Dosing Issues</td>
<td>1. Recalculate doses for individual medications using weight or body surface area.</td>
<td>• Adjust drug doses</td>
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<td>2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions.</td>
<td>• Discontinue or substitute competing medications</td>
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<td>3. Consider drug levels for specific ARV drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).</td>
<td>• Reinforce applicable food restrictions</td>
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<tr>
<td>ARV Drug Resistance</td>
<td>1. Perform resistance testing, as appropriate (see Antiretroviral Drug-Resistance Testing).</td>
<td>• If minimal or no resistance detected to current drugs, focus on improving adherence</td>
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<td>• If resistance to current regimen detected, optimize adherence and evaluate potential for new regimen (see Approach to the Management of Virologic Failure of Antiretroviral Treatment).</td>
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Key to Acronyms: ARV = antiretroviral, cART = combination antiretroviral therapy, DOT = directly observed therapy

References


