Pediatric Antiretroviral Therapy

This chapter provides background information on the general principles of treating HIV-infected children. It outlines some of the challenges and barriers to effective treatment including toxicity, drug-drug interactions, and adherence. Adherence strategies across a spectrum of ages and developmental stages are included in more detail in Chapter 4: *Supportive Care*. Because specific details of treatment are constantly changing, the focus of this chapter is on general principles of management and features unique to pediatrics. Additional details regarding the use of ARV agents and other HIV-related therapies in pediatrics can be found in the federal guidelines.[1] For information on the use of ARV therapy in adolescents and adults, refer to the New York State Department of Health AIDS Institute's (NYSDOH AI) guidelines and the federal guidelines.[2,3]

I. Introduction

Recommendation:

HIV-infected infants or children should be treated by pediatric HIV Specialists. When this is not possible, the treating clinician should seek consultation with a pediatric HIV Specialist (see Appendix I: *HIV Specialist Policy*)**.** (II)

The following clinical care issues are unique to HIV-infected children:

- Age-related differences in virologic, immunologic, and pharmacokinetic parameters
- Differences in tolerability and palatability of pediatric formulations of the medications
- Obstacles associated with adherence to complex regimens
- The dynamics of working with a family unit rather than a single individual

During the first 5 years of the pediatric HIV epidemic, prior to the advent of ARV therapy, clinicians could only deliver palliative care targeting HIV-related complications. As treatment advances were made, monotherapy gave way to combination ARV therapy, which initially consisted of two ARV drugs. In the past few years, these regimens have become more complex, highly active antiretroviral therapy (HAART), consisting of three to four agents, and in some situations, salvage therapy with as many as five to six agents. This historical perspective is important because many children have been treated with sequential courses of monotherapy and combination regimens consisting of two to three ARV drugs. This approach typically caused incomplete suppression of viral replication and selection of resistant virus, thereby complicating the choice and diminishing the likelihood of success of subsequent therapeutic regimens. In addition, our current knowledge of what is the best therapy for children is continually being modified as our understanding of surrogate and clinical markers for disease progression increases and new therapies are developed. The most appropriate therapy for an individual child will depend on multiple factors, including the potency, complexity, and toxicity of the regimen, the child's ability to adhere to the regimen, the child's home situation, and the treatment history. Clinicians should base decisions regarding the best available treatment for an HIV-infected child on data from pediatric clinical trials and, when relevant, data from adult trials.

In contrast to most infections in which eradication of the pathogen requires treatment for a finite period, HIV is a chronic infection requiring treatment for an indefinite period and possibly for

the entire life of the patient. Recent advances in the understanding of the interplay between HIV and the infected host and the discovery of newer ARV agents have resulted in greater optimism and prolongation of wellness. These improved treatments, however, require greater clinician sophistication, greater diligence in medication adherence, and possibly the patient's acceptance of side effects. Although strategic use of drug-drug interactions to affect pharmacokinetic parameters has enhanced treatment efficacy, new agents and their combinations also have resulted in potentially more drug interactions and both short- and long-term toxicities. Medication side effects and complicated regimen schedules continue to make the delivery of safe and effective therapy a challenge.

The most significant advance and success in the pediatric HIV epidemic has been the dramatic reduction in the rates of maternal-infant transmission (for further information, refer to *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*[4]). As a result, there are far fewer HIV-infected infants born in the United States, which limits the ability to perform clinical trials in ARV-naïve children. Therefore, management decisions for pediatric patients often have to be based, at least in part, on results from adult trials. Future clinical trials in children are likely to be small, targeted studies focusing on issues unique to children.

II. Assessment of the HIV-Infected Infant or Child Before Initiating ARV Therapy

Recommendations:

When a child is identified as HIV-infected, the clinician should begin an immediate assessment of the child's clinical and immunologic status, viral burden, resistance profile, and ability to adhere to an ARV regimen. This assessment should be repeated at least every 3 to 4 months to monitor for changes that may necessitate initiating ARV therapy or may affect a child's ability to receive or tolerate ARV therapy. (III)

Before initiating therapy, clinicians should perform a comprehensive physical examination and should obtain a complete history and the following laboratory evaluations: (II)

- **Complete blood count (CBC)**
- **Assessment of kidney and hepatic function**
- **Amylase, lipase, glucose, and lipid profile (total cholesterol, HDL, LDL, and triglycerides)**
- **Viral load**
- **CD4 count and percentage**
- **Resistance profile**

A. Clinical Status

Clinical status should be assessed using the CDC classification system, which categorizes children as clinical class A (mild), B (moderate), C (severe), or N (no symptoms) based on the presence or absence of clinical signs and symptoms of HIV on physical examination, history, or basic laboratory parameters. See Appendix A.

B. Immunological Status

Recommendation:

Clinicians should obtain an assessment of lymphocyte subsets (absolute count and percentage) for HIV-infected infants and children. (II)

Immunologic status should be assessed using the CDC immunologic categories of 1 (no or mild immune suppression), 2 (moderate immune suppression), or 3 (severe immune suppression). These categorizations are based on the child's CD4 count and percentage. See Appendix A.

CD4 counts vary with age. Infants in the first year of life normally have CD4 counts >2000 cells/mm^3, and significant immune compromise would be defined as <1500 cells/mm^3. Regardless of CD4 count, all children in the first year of life should receive PCP prophylaxis. Although the absolute CD4 numbers continue to decrease with age, they do not approach adult normal values until 5 to 6 years of age.

An important finding from multiple clinical trials has been that, despite having relatively high CD4 percentages and numbers, clinically stable children may not demonstrate normal immunologic function. For example, it was shown that only one third of HIV-infected, clinically stable children (mean age, 6 years) who had completed the recommended tetanus immunization schedule had protective levels of tetanus antibody.[5] Similarly, specific immunologic responses against HIV and other recall antigens have been shown to be minimal in this population.

C. Viral Load

RECOMMENDATIONS:

Clinicians should obtain a baseline measurement of plasma HIV-1 RNA copy number (viral load) for all HIV-infected infants and children. (II)

Clinicians should use one assay consistently in a patient because there is significant interassay variability. (I)

The availability of assays that are capable of reliably quantifying the amount of viral RNA in circulating blood has dramatically altered the way providers approach therapy (see Appendix B for a description of the available methodologies for measuring viral load). Specifically, these assays have resulted in the following:

- A better description of the natural history of HIV infection
- The utilization of HIV viral load for predicting disease progression
- The ability to rapidly assess the magnitude and durability of viral suppression resulting from therapy
- Establishment of the gold standard of therapy, which is an undetectable plasma load defined as <400 copies/mL or <40 to 50 copies/mL (with ultrasensitive assay)
- Development of technology that is capable of assessing the genotype and phenotype of the patient's virus to facilitate selection of ARV agents

HIV-1 RNA viral load measurements in serum represent only 2% of the total viral burden; however, the assessment of viral load has proven useful as a prognostic marker in HIV-infected adults and children. During primary HIV-1 infection in adults, there is a burst of relatively uncontrolled viral replication with HIV-1 RNA concentrations of 106 to 107 copies/mL. Within 6 months, newly infected adults establish a lower set point, most often ranging between 104 and 106 copies/mL; the set point has prognostic significance. The lower the viral set point is, the better the patient's prognosis. Over a 10-year study period, untreated adults with <3,000 copies/mL at diagnosis were unlikely to progress to AIDS or death, whereas those with set points >30,000 copies/mL had a median time to an AIDS diagnosis of 2.8 years and a median time to death of 4.4 years.[6]

Studies in HIV-infected infants and children have shown that, in the absence of ARV therapy, children generally have significantly higher viral loads, especially during infancy, than adults.[7] In children not receiving treatment, viral set points vary according to age. During the first 2 months of life, infected infants have RNA levels ranging from 200,000 to >1 million copies/mL.[7] In untreated children, viral load levels slowly decrease over the first 2 years of life (median values remain at >100,000 copies/mL at 18 months of age), although the levels are still higher than adult levels. Children with persistently high levels of plasma HIV-1 RNA, especially infants and younger children with RNA values >750,000 copies/mL, are at risk for

rapid disease progression, opportunistic infections, or irreversible neurologic disease. During a 5-year study period, children >2 years of age with baseline levels of <100,000 HIV-1 copies/mL and CD4 cell percentage >15% were shown to be unlikely to progress to AIDS or death, even in the absence of combination ARV therapy.[8,9] Furthermore, many of these longitudinal studies were performed prior to the widespread use of *Pneumocystis carinii* pneumonia (PCP) prophylaxis. Such therapy has resulted in the dramatic decrease in the incidence of PCP, which further decreases the likelihood of disease progression and death.

Plasma viremia may be transiently affected by intercurrent illnesses, vaccinations, techniques and timing of specimen processing, and immunologic status (i.e., greater variability with lower CD4 counts). Given the large number of variables that may affect viral replication, single measurements should be repeated before making a major treatment decision.

D. Genotypic/Phenotypic Resistance Testing

RECOMMENDATIONS:

Clinicians should obtain resistance testing before initiating treatment in ARV-naïve infants, children, and adolescents or changing a failing regimen for patients already receiving treatment. (II)

Clinicians should consult with an expert for interpretation of resistance testing results. (III)

Resistance testing to determine the susceptibility of a specific viral isolate to ARV agents is a relatively new tool for the identification of the best combination of medications for a patient. The results of resistance testing are most predictable for the agents that the patient is receiving at the time of testing; once a patient stops receiving a drug, the selective pressure that led to a mutation is removed, and overgrowth with wild-type virus may obscure the presence of the resistant virus.

Because an increasing number of newly infected individuals have resistant virus as their initial isolate, resistance assays should be used to help determine an initial regimen, although there are no pediatric-specific data as of yet. Data from studies in adults that affirm the benefit of resistance testing when changing a failing regimen are applicable to children, and use in such circumstances is warranted.[10] However, when the need for medication is urgent or when infants are found to be infected, some experts prefer to initiate medication while the results of the resistance testing are pending.

Interpretation of results is difficult because the mutations that lead to resistance are not yet fully understood. In addition, each of the available test methods has significant limitations and is costly. The New York Medicaid and ADAP reimbursement programs provide reimbursement for three assays (either genotype or phenotype) per year (within 12 months following date of first use). The available test methods are described below.

1. Genotypic Resistance Testing

Genotypic resistance testing requires sequencing selected portions of the viral genome to identify nucleic acid substitutions. This method, typically automated, can assay large numbers of samples and evaluate multiple mutations known to be associated with resistance. Some disadvantages of this methodology are that the automated systems require detectable levels of virus (generally >1000 copies/mL HIV-1 RNA), the mutated (resistant) virus must be at least 20% of the circulating virus population, and the mutations that confer resistance must have been previously described. Mutations that decrease susceptibility to one agent may actually improve susceptibility to another. For example, the RT mutation M184V dramatically decreases virus susceptibility to lamivudine but modestly increases susceptibility to zidovudine. Such mutational interactions can best be evaluated using a phenotypic resistance assay.

One method of genotypic testing establishes a patient's genotype, and then predicts susceptibility by comparing a patient's viral genotype to those in a large data set of viral isolates with correlated genotypic and phenotypic data.

2. Phenotypic Resistance Testing

Phenotypic resistance testing is labor-intensive and requires separate assays for each agent. Turnaround time is considerably longer than that for genotypic assays. It is also considerably more expensive than genotypic testing.

Phenotypic resistance testing requires using recombinant virus in the presence of therapeutic levels of the ARV agent of interest. Segments of reverse transcriptase and protease that are important for resistance are inserted and amplified into a laboratory HIV isolate, which is then grown *in vitro* in the presence of the medications. Replicative capacity measurements may appear with phenotypic testing results, but there are no data regarding the clinical utility of this measurement.

E. Potential Barriers to Treatment Adherence

RECOMMENDATIONS:

Clinicians should identify and address potential barriers to adherence with caregivers and patients before initiating a regimen. (II)

The clinician should discuss the importance of consistent adherence to the ARV regimen with the child in an age-appropriate way. (III)

If adherence barriers cannot be overcome, the clinician and family may choose to defer treatment. (III)

Discussions about successful implementation of a treatment regimen are especially important because incomplete adherence may be more harmful than not starting the medication at all. In order to assess a caregivers and patient's ability to adhere to an ARV regimen, the clinician needs to identify potential barriers for each individual patient. For example, if the caregiver is concerned that the ARV medications will harm the child, he/she may not adhere to the regimen. The clinical team should also be aware of medical, psychiatric, psychological, or cognitive limitations of the caregiver who is responsible for supervising (for an older child/adolescent) or administering (to a younger child) a complicated medical regimen.

Table 1 lists potential barriers that need to be addressed before beginning a treatment regimen. Multiple meetings with the caregiver may be necessary to explain these issues before starting or changing therapy. The family's and patient's understanding and perception of HIV infection are important factors in adherence to a therapeutic regimen.

TABLE 1
POTENTIAL BARRIERS TO ADHERENCE

The following potential barriers should be assessed and addressed before initiating ARV therapy:

- Communication difficulties due to language, literacy, or differing beliefs
- Unstable living conditions (lack of housing, food, childcare)
- Discomfort with disclosure of HIV status
- Inadequate education about disease and medications
- Challenges regarding access to healthcare
- Medical, psychiatric, psychological, or cognitive limitations of the caregiver or child
- Foster care/consent
- Potential interference with activities of daily living, especially school, meals, etc.

For more information on adherence issues and strategies that are specific to pediatric patients, see Chapter 4: *Supportive Care*.

III. Deciding When to Initiate ARV Therapy

Recommendations:

The clinician should discuss the risks and benefits of a treatment regimen with HIV-infected children and their caregivers, allowing them to make an informed decision regarding initiating therapy. If the potential risks outweigh the benefits, the clinician and family may choose to defer treatment. (III)

In most cases, clinicians should initiate treatment soon after HIV infection is identified in an infant, either immediately or as soon as the resistance profile is available. (III)

Clinicians should initiate treatment in children older than 1 year of age with symptomatic disease or advancing immunosuppression (see Table 2)**.** (II)

Multiple factors influence the decision as to the optimal time to initiate ARV treatment in a treatment-naïve, HIV-infected child. This decision has become more complicated due to 1) the rapid development of new drugs, each with distinct safety and efficacy parameters, which may be altered when used in combinations, and 2) the recognition that strict adherence is essential for long-term efficacy. There are little available data regarding the optimal time to initiate ARV therapy in pediatric populations.

Initiating treatment early is supported by the finding that a durable suppression of virus is more likely in the presence of a more intact immune system and a lower viral load at baseline.[11] In addition, effective early treatment allows normal immune maturation or preservation of immune function and better growth and development.[12] It has also been speculated that durable suppression of virus would be more easily attained early in life because the child would be infected with a more homogeneous population of HIV-1. The subsequent challenge is to maintain viral suppression for extended periods of time with acceptable toxicity.

Infants

The Committee recommends treating almost all infants as soon as they are identified as HIV-infected, even in the absence of symptoms and with normal CD4 cell numbers. This approach is based on the observation that some HIV-infected infants may demonstrate early and rapid disease progression in the first year of life and that this progression is frequently not predictable using surrogate markers such as CD4 enumeration and/or viral loads. Early initiation of therapy can lead to prolonged virologic suppression, immune preservation, clinical stability, and normal growth velocity and cognitive development. Other experts have recommended deferring therapy in asymptomatic infants with low viral loads and good immune function; however, this Committee concluded that therapy for infants should rarely be deferred except in cases in which a family absolutely cannot or will not adhere to the HAART regimen. In rare cases, some clinicians would defer treatment in infants who have good clinical, immunologic, and virologic parameters based on the concern that adherence is particularly difficult for mothers who just discovered that their infant is HIV-infected.

Children >1 year of age

When children are identified as being HIV-infected after 1 year of age, laboratory and clinical markers provide useful prognostic information. Children beyond the neonatal period with HIV RNA <100,000 copies/mL and normal-for-age CD4 parameters are unlikely to experience clinical progression over a 5-year period.[8] A history of normal growth and development further assures that the child will not experience rapid disease progression. The clinical history and clinical, immunologic, and virologic status at the time of diagnosis should be considered when evaluating the risks and benefits of initiating ARV therapy in children older than 1 year of age (see Table 2). The clinician needs to discuss the pros and cons of initiating therapy with the family. Because viral eradication is not attainable with current therapy, consideration should be given to the fact that treatment may be required for life.

Table 2 Indications for Initiating ARV Therapy in HIV-Infected Children ≥1 Year of Age						
Clinical Category		**CD4 Percentage**		**Plasma HIV RNA Copy Number**		**Recommendation**
AIDS (Clinical category C)*	***OR***	<15% (Immune Category 3)*		Any value		Initiate ARV therapy
Mild-Moderate symptoms (Clinical category A or B)*	***OR***	15-25%† (Immune Category 2)*	***OR***	>100,000 copies/mL‡		Consider initiating ARV therapy
Asymptomatic (Clinical category N)*	***AND***	>25% (Immune Category 1)*	***AND***	<100,000 copies/mL‡		Many experts would defer therapy and closely monitor clinical, immune, and viral parameters for deterioration

Modified from the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* developed by The Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Pediatric and Family HIV Resource Center (NPHRC), The Health Resources and Services Administration (HRSA), and The National Institutes of Health (NIH). June 25, 2003.

* See Appendix A.

† Many experts would initiate therapy if CD4 cell percentage is between 15% and 20% and defer therapy with increased monitoring frequency in children with CD4 cell percentage 21% to 25%.

‡ There is controversy among pediatric HIV experts regarding the plasma HIV RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV RNA levels were between 50,000 to 100,000 copies/mL.

Indications for initiation of ARV therapy in post-pubertal HIV-infected adolescents should follow the adult guidelines (see the NYSDOH AI guidelines[2] and the federal guidelines[3]).

IV. Initiating and Selecting an ARV Regimen

Recommendations:

ARV treatment should be initiated and/or changed by a pediatric HIV Specialist who is experienced with the issues that distinguish pediatric patients from adults (see Appendix I: *HIV Specialist Policy*)**.** (III)

Clinicians should obtain a maternal and infant (or child) ARV treatment history and should assess the resistance profile in the context of the ARV history before choosing a regimen. (II)

The clinician should initiate an ARV regimen of at least three drugs, including two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) (see Table 4 for recommended regimens and Appendix C for formulations and dosages for each drug)**.** (II)

> **Key Point:**
>
> Many of the newer FDA-approved ARV drugs have been released on the market without specific pediatric formulations; however, pediatric clinicians should still consider using these drugs as part of their armamentarium after consulting with a pediatric HIV Specialist.

The available ARV therapies that have been approved by the Food and Drug Administration (FDA) are categorized in four classes:

- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI, NtRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Fusion inhibitors (FI)

Although each agent in a class has similar mechanisms of action and overlapping toxicities, each also has unique features that need to be considered, including pharmacokinetic parameters, drug-drug interactions, palatability, toxicities, and HIV mutations associated with drug resistance. Unique drug-drug interactions are frequently exploited to enhance the pharmacokinetic parameters of some therapies. For example, ritonavir increases drug exposure to other PI agents, allowing either increased intervals between doses or decreased amounts of administered drug, by increasing the trough levels and/or the drug exposure as measured by the area under the concentration versus time curve (AUC).

Key Point:

In HIV-infected children, especially infants, drug-drug interactions and pharmacokinetic parameters related to age/developmental stage should be considered when selecting components of the treatment regimen. In some children, the doses may exceed those recommended for HIV-infected adults.

The goal of therapy needs to be individualized for each child. Clinicians should consider both the child's and the family's ability to adhere to the proposed regimen. When initiating ARV therapy, all resources to maximize adherence should be mobilized. Specific measures, such as clearly detailing the treatment schedule, electronic devices, pill boxes, telephone calls, and home visits, should be used as appropriate. Additional counseling sessions are advised when new medications are started or when current regimens are altered. When possible, treatment regimens should be tailored to ease administration (see Table 3). For more information on facilitating adherence, see Chapter 4: *Supportive Care*; for adherence issues particular to HIV-infected adolescents, refer to Chapter 3: *Identification and Ambulatory Care of Adolescents*.

TABLE 3
DRUG-RELATED CONSIDERATIONS WHEN CHOOSING AN ARV REGIMEN

Ease of Administration

- Availability and palatability of a pediatric formulation
- Patient's ability to swallow pills/soft gel caps
- Frequency of dosing (qd, bid, tid, qid)
- Food effects
- Storage requirements (e.g., refrigeration)

Safety and Efficacy

- Age-related pharmacokinetics
- Efficacy of therapeutic regimen
- Durability of antiretroviral effect
- Drug interactions
- Adverse reactions
- Safety in pregnancy (for female adolescents)
- Likelihood of resistance

When a decision is made to initiate therapy in a child, initial regimens should include two NRTIs in combination with an NNRTI or a PI (see Table 4). Choosing a particular regimen will depend on a multitude of factors, especially those listed in Table 3. Treatment regimens used in children are often based on data from adult clinical trials. Ideally, clinical trials will occur in children as well, but as the population of newly infected young children diminishes in this country, some information may need to be gleaned from adult trials.

TABLE 4
RECOMMENDED ARV REGIMENS FOR INITIAL THERAPY FOR HIV-INFECTED CHILDREN

Zidovudine or Stavudine	+	Lamivudine or Didanosine	+	Nelfinavir or Lopinavir/r or Efavirenz

* Stavudine and didanosine should only be used in combination when no other options are available.

Although considered less ideal than the above regimens, once daily therapy may be necessary for some children and adolescents for whom adherence is a challenge. The following regimens could be used once a day:

Didanosine-EC or Tenofovir	+	Lamivudine or Emtricitabine	+	Efavirenz or Atazanavir + Ritonavir or Fosamprenavir (or amprenavir) + Ritonavir

Additional useful drugs often used in children with resistant virus or who cannot tolerate the above combinations include:

Abacavir, Nevirapine, Saquinavir, Indinavir, Enfuvirtide

Often, the provider will tailor the initial regimen based on the resistance profile of the child's virus. The following caveats apply to the above medications:

- Monotherapy should never be used except in pregnant women with low viral loads.
- *Efavirenz* is not yet approved for children under 3 years. *Efavirenz* is associated with neural tube defects in infants exposed to it in utero. Before initiating *efavirenz* in female adolescents, clinicians should be certain that the patient is not pregnant, is not planning on becoming pregnant, and is using effective contraception.
- *Nevirapine* should not be initiated in females with CD4 counts >250 cells/mm^3 or males with CD4 counts >400 cells/mm^3 because it has been linked to severe rapidly progressing liver failure and death in this population. When no other feasible alternatives exist, an HIV Specialist should be consulted.
- *Tenofovir, emtricitabine,* and *atazanavir* are not yet approved for children under 18 years.
- *Amprenavir* oral solution should not be given to children under 4 years.
- *Saquinavir* and indinavir are not yet approved for children under 13 years.
- *Enfuvirtide* is not yet approved for children under 6 years.
- To avoid reduction of *atazanavir* absorption, atazanavir should not be given within 30 minutes of didanosine.
- When given in combination with *efavirenz* or *tenofovir, atazanavir* must be given with ritonavir-boosting.
- S*aquinavir, indinavir, atazanavir,* and, to a lesser-degree, *amprenavir* are generally given with ritonavir-boosting to enhance pharmacokinetics and allow lower and less frequent dosing. *Saquinavir* hard-gel capsules should never be given without ritonavir.
- *Zidovudine* and *stavudine* should never be given together.
- *Delavirdine* and *zalcitabine* are not approved for children and do not offer anything that warrants their off-label use except in the most unusual circumstances. They should rarely if ever be used in children.
- *Abacavir* can lead to a hypersensitivity reaction that can be fatal upon rechallenge.

V. Follow-Up Monitoring for Patients Receiving ARV Therapy

Recommendations:

Children receiving HAART should be followed by a pediatric HIV Specialist either as their primary care clinician or through consultation with their primary care clinician. (II)

Clinicians should either contact patients/caregivers by phone or arrange to see them in person 1 to 2 weeks after initiating therapy to monitor adherence and assess for side effects. (III)

A. Monitoring for Efficacy

Recommendations:

Clinicians should obtain a repeat viral load within 4 to 6 weeks after initiating or changing ARV therapy. If there is no decrease in viral load, adherence should be reviewed. (III)

Clinicians should routinely obtain lymphocyte subsets and viral load every 3 to 4 months. Children with significant ongoing viral replication may require more frequent monitoring. (II)

Clinicians should repeat all tests that suggest a significant change (either positive or negative) in plasma RNA copy numbers. (III)

CD4 percentages show less age variability and are typically used to measure changes in CD4 levels across different ages. During all periods of childhood, it is preferred to maintain a CD4 percentage >25%. Repeated enumeration of CD4 cell numbers may not be helpful in individuals with extremely low CD4 cell numbers and advanced disease.

Numerous studies show that children who are adherent to HAART can achieve suppression of viral replication to below detectable levels and can gain concurrent clinical and immunologic benefit.[11,12] However, the presence of an undetectable viral load in peripheral blood does not mean that the virus has been eradicated from the peripheral circulation or other reservoirs, such as lymphoid tissue, the gastrointestinal tract, and the central nervous system.

There is also evidence suggesting that patients who respond only partially to ARV therapy can still gain clinical and immunologic benefit even when complete viral suppression is not achieved.[13] Prolonged viral suppression can prevent or delay the development of ARV-resistant mutations.

> **Key Point:**
>
> The goal of ARV therapy should be an undetectable plasma viral load, which is defined as <400 copies/mL or <40 to 50 copies/mL (with ultrasensitive assay). If this is not achievable, realistic expectations of available therapy should dictate an acceptable level of viremia for each child.

B. Monitoring for Toxicities and Side Effects

Recommendations:

Clinicians should perform a history, physical examination, and laboratory monitoring for toxicity within 4 weeks after initiating ARV therapy, and should repeat these at least every 3 months in children receiving ARV therapy. (II)

Laboratory assessments for toxicity should include CBC, assessment of renal and hepatic function, amylase, lipase, and glucose. (II)

When nevirapine is initiated, the clinician should obtain serum liver enzymes every 2 weeks until 6 weeks after initiating therapy, and then monthly for 3 to 4 months. (II)

Screening of serum cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein should be performed in HIV-infected children initiating HAART, 3 to 6 months after initiation, and approximately every 6 months thereafter. Abnormal results warrant repeat studies performed in the fasting state. (II)

Clinicians should assess lactic acid levels in patients receiving NRTIs who develop clinical manifestations (abdominal pain, anorexia, nausea/vomiting, hyperventilation, and/or myalgias) or laboratory markers suggestive of lactic acidosis. (II)

All the available ARV agents have significant potential toxicities. Interactions between ARV agents and other drugs that may be used in HIV-infected children can lead to additional and potentially more severe reactions. Careful monitoring should occur and includes laboratory as well as clinical assessments. Although adverse events can occur at any time, even after years of treatment, problems are usually noted in the first few weeks or months after starting a new drug. For some of the well-described drug toxicities, the initial symptoms may mimic other diagnoses. This can lead to a delay in diagnosis in cases in which the relationship between the adverse event and the drug were not recognized promptly.

Short- and long-term toxicities include abnormal fat distribution, hyperlipidemia, mitochondrial toxicity, hypersensitivity reactions, peripheral neuropathy, liver toxicity, diabetes, renal toxicity, anemia, neutropenia, pancreatitis, and diarrhea.

Key Point:

Although some adverse events do not warrant stopping therapy, others, such as a hypersensitivity reaction to abacavir or hepatitis associated with nevirapine, require prompt recognition of symptoms and permanent interruption of the drug. Failure to recognize these symptoms may lead to death.

Chronic compensated lactic acidemia can occur during treatment with NRTIs. Although symptomatic decompensated lactic acidemia with hepatomegaly and hepatic steatosis is rare (approximately 1 case in 1000 person-years), the condition may be fatal. The clinical features of lactic acidemia are nausea, vomiting, abdominal pain, and weight loss. Hepatic involvement is common and includes hepatomegaly, ascites, encephalopathy, elevation of liver enzymes, and hepatic steatosis. Hepatic necrosis has been reported in fulminant cases. The postulated pathogenesis of lactic acidemia is through mitochondrial toxicity. Although nearly all reports of NRTI-associated mitochondrial dysfunction with lactic acidosis are in adult patients, children are not free of risk for this disorder.[14] Fatal lactic acidemia reported in two pregnant women receiving dual NRTI therapy with stavudine and didanosine may indicate that women, especially during pregnancy, have a greater risk.[15] Assessment of lactic acid is warranted in individuals receiving NRTIs who develop clinical manifestations suggestive of lactic acidosis. It has been suggested that levels >2.5 mmol/L are abnormal and warrant repeating. In symptomatic individuals with levels >4 mmol/L, discontinuation of NRTIs may be required. Supportive measures and cessation of NRTIs have resulted in recovery.[14] Currently, however, routine monitoring of lactic acid levels is not generally recommended because of the rarity of symptomatic lactic acidemia and the frequency of falsely elevated lactic acid levels due to the significant technical problems in obtaining specimens.

For a list of specific toxicities that have been observed with the use of particular ARV agents, the clinician should refer to the federal guidelines.[1]

C. Monitoring Adherence

RECOMMENDATIONS:

The clinician should regularly discuss the importance of consistent adherence to the ARV regimen with the caregiver and the child in an age-appropriate way. (III)

At each visit, clinicians should assess adherence in children and adolescents receiving ARV therapy. In cases in which adherence becomes problematic and cannot be resolved, simplification or discontinuation of therapy should be included as a potential management strategy. (III)

> **Key Point:**
>
> Challenges of adherence change as HIV-infected children age and enter different developmental stages.

While a child is receiving therapy, clinicians should continue monitoring adherence because both anticipated (e.g., changes in developmental stages) and unforeseen circumstances (e.g., change in care provider, acting out behavior) frequently occur. For more information on adherence issues and strategies that are specific to pediatric patients, see Chapter 4: *Supportive Care*.

VI. CHANGING HAART REGIMENS

RECOMMENDATIONS:

Decisions regarding changing therapy should be individualized and should be made in consultation with a pediatric HIV Specialist. (III)

The clinician should decide whether to change therapy, or modify or continue the present regimen in any of the following circumstances: (III)

- **Clinical progression**
- **Sustained increase in viral load**
- **Progressive immunodeficiency**
- **Significant toxicity**
- **Significant unmodifiable adherence issues have developed with the current regimen**

When new regimens are selected because of virologic failure, the clinician should perform resistance testing while the child is still on the failing regimen (see Section II. D. *Genotypic/Phenotypic Resistance Testing*)**.** (II)

When the regimen is changed because of virologic failure, clinicians should switch all drugs at the same time. Ideally, the new regimen should have three new active drugs that the child has not previously taken and that are not cross-resistant to medications the child has taken. (II)

The clinician should discuss the risks and benefits of the specific medications under consideration with the family and child when changing treatment. (III)

> **Key Point:**
>
> When virologic suppression has been achieved but therapy needs to be changed because of toxicity, one drug may be substituted for another provided that the new drug is of equal potency.

Considerations when deciding whether to change therapy:

- Previous ARV therapy and resistance profile
- Likelihood of adherence (see Section VI: The Importance of Treatment Adherence)
- Clinical and immunologic status
- The child's ability to take and tolerate the medications
- The likelihood of achieving complete viral suppression
- The possibility of toxicities or drug-drug interactions.

Clinicians should consider changing therapy following a significant increase in virus replication (> 0.5 log), sustained plasma RNA values in excess of 50,000 to 100,000 copies/mL, a significant decrease in CD4 percentage, or significant toxicity.

When changing therapy, the clinician should choose a treatment regimen consisting of multiple drugs to which that child is naïve. Genotypic and phenotypic resistance testing are useful in these circumstances and should be obtained while the patient is still receiving therapy.[10] A new regimen is occasionally selected for children with limited previous experience based on history alone. However, for children with extensive previous treatment history and limited switch options, it is general practice to use genotypic or phenotypic resistance testing information plus the patient's ARV history to choose a new regimen. ARV therapy-experienced children are likely to carry quasi-species of HIV-1 containing genetic mutations associated with resistance to some or all of the previously used classes.

The decision to change therapy should take into account the findings that continued HIV replication in the presence of ARV therapy facilitates selection of resistant virus, which may demonstrate cross-resistance with multiple agents within the same class of therapies. Similarly, if medications are switched and the new combination does not completely suppress virus replication, new mutations in the virus will occur. At that point, subsequent control of viremia would become even more difficult. Alternatively, some clinicians would wait until new agents become available. Therefore, when the risks and benefits of switching therapy are considered, these issues, as well as adherence, toxicity, the child's ability to take multiple therapies, and drug-drug interactions, should be taken into consideration.

Many children who have been on long-term ARV therapy experience treatment fatigue. This occurs as the thought of having to take medication for many years, and possibly the rest of their lives, becomes overwhelming, particularly to pre-adolescents and adolescents. Often these children experience a rebound in viral load, and clinicians later discover that this is a result of diminished adherence. In patients with good clinical and immunologic function, some clinicians accept a temporary discontinuation of ARV therapy with very close monitoring of viral load and CD4 cell counts. The rationale is that a complete discontinuation of ARV therapy will maintain viral sensitivity and prevent the development of resistance that would occur with partial or intermittent discontinuation. No data exist to support or discredit this theory.

VII. Special Considerations for ARV-Experienced Children Who Are Naïve to PIs and NNRTIs

Many pediatric HIV clinicians manage children who have been treated with non-HAART regimens (e.g., dual nucleosides) for extended periods of time and have continued to be clinically well with fairly low copy numbers and relatively intact CD4 cell counts. For these children, one acceptable approach may be to allow low levels of viremia while maintaining a stable immunologic profile and to wait for a more appropriate therapeutic option to develop. However, continued viral replication in the presence of ARV medications ultimately leads to selection of resistance mutations to those agents.

VIII. PI- and NNRTI-Experienced Children: Salvage Therapies

Recommendation:

The choice of salvage therapy in PI- and NNRTI-experienced children should be made on a case-by-case basis and should be guided by the child's ARV history, resistance profile, and ability to adhere to a regimen. (III)

Despite having been treated with PIs, NNRTIs, and NRTIs, a growing number of HIV-infected children have not been able to sustain viral replication below the level of quantification. Although incomplete adherence may be a factor in some of these cases, other contributors include the previous use of these agents in the child (i.e., sequential mono or dual therapies or addition of new agents without changing the entire regimen), inadequate dosing due to poorly described pharmacokinetic parameters, and toxicity management. In these cases, the pros and cons of continuing an ARV treatment regimen instead of switching to an alternative treatment regimen need to be closely considered and discussed with the child and family.

There is no consensus regarding the best approach to treat these patients. Choice of the new regimen should be guided by the child's ARV history and results from resistance assays. If the child has been exposed to PIs, NNRTIs, and NRTIs, it is unlikely that a simple three- or even a four-drug regimen will sustain suppression of virus to undetectable levels. In this setting, viremia alone, in the face of stable clinical and immunologic status, does not require a medication change in a heavily pre-treated child.

None of the following approaches have been validated in large-scale pediatric clinical trials; however, they constitute the most reasonable approaches to a difficult problem, which may be ameliorated in the future by the development of new ARV agents.

- Continuing a regimen that allows viral replication at a level that will not cause additional immunologic or clinical deterioration while waiting for newer therapeutic approaches and agents to be developed. This strategy may involve simplification of the regimen, such as stopping the PI or NNRTI component of the regimen.
- Choosing an aggressive regimen of four to six agents in an attempt to suppress viral replication to undetectable levels with an acceptable level of toxicity. This regimen may contain two NRTIs, an NNRTI, two to three PIs, and enfuvirtide (for patients older than 6 years of age).
- Withholding ARV therapy for a period of time in the expectation that while the child is not receiving therapy, the wild-type virus may outgrow resistant viruses and again predominate. After this interim period, an aggressive regimen can then be initiated. *There are limited clinical data on this approach in adults and children, and it should be used with extreme caution, especially in children with significant immune suppression.* It is expected that resistant virus is archived in the genome of the patient's cells and will reappear in due time.

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Appendix A

CDC Clinical and Immunologic Status Classifications

Table A-1 Immunologic Categories for HIV-Infected Children Based on Age-Specific CD4 T-Lymphocyte Counts and Percentage of Total Lymphocytes			
Immunologic Category	**Age**		
	<12 months cells/mm³ (%)*	**1-5 years cells/mm³ (%)***	**6-12 years cells/mm³ (%)***
Category 1: No suppression	≥1,500 (≥25)	≥1,000 (≥25)	≥500 (≥25)
Category 2: Moderate suppression	750-1,499 (15-24)	500-999 (15-24)	200-499 (15-24)
Category 3: Severe suppression	<750 (<15)	<500 (<15)	<200 (<15)

Modified from the Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994;43:1-10.

* Percentage of total lymphocytes

Table A-2
1994 Revised HIV Pediatric Classification System Clinical Categories

Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A

Category A: Mildly Symptomatic

Children with two or more of the following conditions but none of the conditions listed in Categories B and C:

- Lymphadenopathy (> 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately Symptomatic

Children who have symptomatic conditions other than those listed for Categories A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to the following:

- Anemia (<8 gm/dL), neutropenia (<1,000 mm^3), or thrombocytopenia (<100,000 mm^3) persisting >30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e., thrush) persisting for >2 months in children aged >6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before age 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting >1 month
- Toxoplasmosis with onset before age 1 month
- Varicella, disseminated (i.e., complicated chickenpox)

Category C: Severely Symptomatic

- Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a Category B condition)

Adapted from the Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994;43:1-10.

Appendix B

Available Methodologies for Measurement of Viral Load and Interpretation of Results

Current methodologies that measure viral load include the polymerase chain reaction (PCR), branched chain DNA (bDNA) amplification, and nucleic acid sequence-based analysis (NASBA).

No single RNA quantitation assay has been shown to be superior. The PCR, bDNA, and NASBA assays quantify the amount of replicating virus present in the plasma at a given time with results reported as HIV copy numbers/mL of plasma. Each method has different blood volume and anticoagulant requirements and slightly different characteristics with regard to reproducibility. At the present time, non-B clade HIV subtypes are usually assessed by bDNA assays; however, new PCR assays are sensitive and specific for non-B clade HIV subtypes. If this technology is available, there would be no need to use the bDNA assay. Although many investigational studies used a cutoff of 400 copies/mL as "undetectable," assays that can quantify virus at levels of 40 or 50 RNA copies/mL have become available and are commonly used in clinical practice.

When interpreting plasma RNA copy numbers, the intra-assay standard deviation is between 0.15 and 0.3 $\log_{10}$. For an individual child, less than a 0.5 $\log_{10}$ (3-fold) change may represent assay variability and not true biologic difference. Table 1 uses a hypothetical patient with a starting viral copy number of 100,000 copies/mL to illustrate how viral load reductions can be expressed in different terms.

Table B-1
Viral Load Reduction Conversions*

Viral Load Reduction From Baseline	Viral Load Reduction From Baseline	Viral Load Reduction From Baseline	Remaining Viral Load Number
0.3 log	50.0%	2-fold	50,000 copies/mL
0.5 log	75.0%	3-fold	25,000 copies/mL
0.7 log	80.0%	5-fold	20,000 copies/mL
1.0 log	90.0%	10-fold	10,000 copies/mL
1.5 log	96.8%	32-fold	3,200 copies/mL
2.0 log	99.0%	100-fold	1,000 copies/mL
2.5 log	99.7%	316-fold	300 copies/mL
3.0 log	99.9%	1,000-fold	100 copies/mL

* In a hypothetical patient with a starting viral load of 100,000 copies/mL.

APPENDIX C

AVAILABLE ANTIRETROVIRAL DRUGS

Because dosing requirements vary greatly based on concurrent medications and age of patient, dosing for an individual patient should be checked with the federal *Pediatric Antiretroviral Guidelines* and a pediatric HIV Specialist.

TABLE C-1 NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS: PREPARATIONS AND DOSING	
Abacavir, ABC *(Updated December 2008)* (Ziagen)	
Form	300-mg scored tablets 20-mg/mL oral solution
Dosing Recommendations	Perform commercially available pharmacogenetic testing for the HLA-B*5701 allotype (associated with a predisposition to abacavir hypersensitivity) before prescribing abacavir; do not give abacavir if HLA-B*5701 positive. If using 300-mg scored tablet: ≥14 to 21 kg: ½ tablet AM and PM (total daily dose 300 mg) >21 to <30 kg: ½ tablet AM, 1 tablet PM (total daily dose 450 mg) ≥30 kg: 1 tablet AM and PM (total daily dose 600 mg) Max: 300 mg q12h or 600 mg q24h
Adverse Events	*More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia. *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions have been associated with ABC in approximately 5% of adults and children (rate varies by race/ethnicity; majority of reactions in those with HLA-B*5701 allele). Hypersensitivity to ABC is a multi-organ clinical syndrome usually characterized by a sign or symptom in >2 of the following groups: 1) fever; 2) rash; 3) gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain; 4) constitutional, including malaise, fatigue, or achiness; and 5) respiratory, including dyspnea, cough, or pharyngitis. This reaction generally occurs in the first 6 weeks of therapy and has occurred after a single dose. **Patients suspected of having a hypersensitivity reaction should have ABC stopped and NOT RESTARTED BECAUSE HYPOTENSION AND DEATH HAVE OCCURRED UPON RECHALLENGE.** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis may occur.
FDA Pregnancy Category	C

Didanosine, ddI *(Updated November 2008)* (Videx; Videx EC)	
Form	Videx: powder for oral solution, to make 10 mg/mL Videx EC: 125-, 200-, 250-, 400-mg enteric coated, delayed-release capsules
Dosing Recommendations	*Oral solution* 2 wk-8 mo: 100 mg/m^2/dose q12h 8 mo-12 y: 120 mg/m^2/dose q12h (90-150 mg/m^2/dose q12h)[a] ***or*** *Capsules* 20 to <25 kg: 200 mg q24h 25 to <60 kg: 250 mg q24h ≥60 kg: 400 mg q24h Dose adjustment needed if used in combination with tenofovir
Adverse Events	*More common:* Diarrhea, abdominal pain, nausea, and vomiting. *Less common (more severe):* Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis (dose related, less common in children than adults).
FDA Pregnancy Category	B
Emtricitabine, FTC *(Updated November 2008)* (Emtriva)	
Form	200-mg capsules 10 mg/mL oral solution
Dosing Recommendations	≥3 mo: 6 mg/kg/dose/day Max: 240 mg oral solution ***or*** 200-mg caps q24h (Capsules may be used if BW >33kg)
Adverse Events	*More common:* Headache, insomnia, diarrhea, nausea, rash, and skin discoloration (hyperpigmentation on palms and/or soles, predominantly observed in non-Caucasian patients). *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. In patients co-infected with HIV and HBV, exacerbations of hepatitis have occurred when changes have been made from FTC-containing regimens to non-FTC-containing regimens.
FDA Pregnancy Category	B
Lamivudine, 3TC *(Updated November 2008)* (Epivir)	
Form	150-, 300-mg tablets 150-mg scored tablets 10-mg/mL oral solution (Also available as Epivir HBV, 100-mg tablets and 5 mg/mL oral solution)[b]
Dosing Recommendations	<30 d: 2 mg/kg/dose q12h ≥1 mo: 4 mg/kg/dose q12h

	If using 150-mg scored tablet: 14 to 21 kg: ½ tablet AM and PM (total dose 150 mg) >21 to <30 kg: ½ tablet AM, 1 tablet PM (total dose 225 mg) ≥30 kg: 1 tablet AM and PM (total dose 300 mg) Max: 150 mg q12h or 300 mg q24h
Adverse Events	*More common:* Headache, fatigue, and nausea, which generally decrease over time; decreased appetite, diarrhea, skin rash, and abdominal pain. *Less common (more severe):* Pancreatitis (primarily seen in children with advanced HIV infection receiving other additional medications), peripheral neuropathy, anemia, decreased neutrophil count, increased liver enzymes, and fat redistribution. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. In patients co-infected with HIV and HBV, exacerbations of hepatitis have occurred when changes have been made from 3TC-containing regimens to non-3TC-containing regimens.
FDA Pregnancy Category	C
Stavudine,[c] d4T *(Updated November 2008)* (Zerit)	
Form	15-, 20-, 30-, 40-mg capsules 1-mg/mL oral solution
Dosing Recommendations	0-1 mo: 0.5 mg/kg/dose q12h 1 mo-12 y: 1 mg/kg/dose q12h (Max: 30 mg q12h) ≥13 y: 30-60 kg: 30 mg q12h ≥60 kg: 40 mg q12h
Adverse Events	*More common:* Headache, gastrointestinal disturbances, skin rashes, and lipoatrophy. *Less common (more severe):* Peripheral neuropathy, pancreatitis, and lipodystrophy/lipoatrophy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. The combination of d4T with didanosine (ddI) may in enhanced toxicity (increased risk of fatal and fatal cases of lactic acidosis or pancreatitis); this combination should not be used unless the potential benefits clearly outweigh the potential risks. Rarely, increased liver enzymes; rapidly progressive ascending neuromuscular weakness.
FDA Pregnancy Category	C
Tenofovir, TDF *(Updated March 2010)* (Viread)	
Form	300-mg tablets
Dosing Recommendations	<12 y or <35 kg: Not yet approved; clinical trials data support 8 mg/kg q24h for age <8y, and 210 mg/m^2 q24h for 8-12 y of age (Max: 300 mg q24h) ≥12 y and ≥35 kg: 300 mg q24h
Adverse Events	*More common:* Nausea, diarrhea, vomiting, and flatulence. *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. TDF caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. Decreases in bone mineral density have been shown in both adults and children taking TDF for 48 weeks; the clinical significance of these changes is

	not yet known. Evidence of renal toxicity, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate has been observed in animal studies at high exposure levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored.
FDA Pregnancy Category	B
Zidovudine,[c] ZDV, AZT *(Updated November 2009)* (Retrovir)	
Form	100-mg capsules 300-mg tablets 10-mg/mL oral solution
Dosing Recommendations	Premature infants: For neonates <30 wks gestational age: 1.5 mg/kg IV or 2 mg/kg q12h orally, increased to q8h at 4 wks of age For neonates ≥30 wks gestational age: 1.5 mg/kg IV or 2 mg/kg q12h orally, increased to q8h at 2 wks of age 0-1.5 mo: 2 mg/kg/dose q6h orally or 1.5 mg/kg IV q6h 1.5 mo-13 y: 180-240 mg/m^2/dose 12h (Max: 300 mg q12h) ≥13 y: 300 mg q12h or 200 mg q8h (Max: 300 mg q12h) Or by body weight: 4 to <9 kg: 12 mg/kg q 12h 9 to <30 kg: 9 mg/kg q12h >30 kg: 300mg q12h
Adverse Events	*More common:* Hematologic toxicity, including granulocytopenia and anemia, and headache. *Less common (more severe):* Myopathy, myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.
FDA Pregnancy Category	C
Combination NRTI	
Name Agents Strength	**Combivir** ZDV/3TC (300/150)
Dosing Recommendations	≥13 y: 1 tablet twice daily
Name Agents Strength	**Trizivir**,[d] ZDV/3TC/ABC (300/150/300) [see abacavir for comments on HLA-B*5701 testing]
Dosing Recommendations	≥13 y: ≥40 kg: 1 tablet q12h <40 kg: not recommended

Name Agents Strength	**Truvada** TDF/FTC (300/200)
Dosing Recommendations	≥18 y: 1 tablet once daily
Name Agents Strength	**Epzicom** ABC/3TC (600/300) [see abacavir for comments on HLA-B*5701 testing]
Dosing Recommendations	≥13 y: 1 tablet once daily
Combination NRTI/NNRTI	
Name Agents Strength	**Atripla** TDF/FTC/EFV (300/200/600)
Dosing Recommendations	≥18 y: 1 tablet once daily (administer on an empty stomach, preferably at bedtime)

[a] May need higher dose in patients with CNS disease.

[b] Epivir HBV oral solution and tablets contain a lower amount of lamivudine than Epivir oral solution and tablets. Epivir HBV is only FDA approved for use in treatment of HBV infection or HIV/HBV co-infection. The Epivir HBV tablet is appropriate to use in the treatment of HIV in a child requiring the 100-mg dose when a tablet formulation is preferred.

[c] Stavudine and zidovudine should never be given together because of drug interactions.

[d] Trizivir should not be used in patients with renal insufficiency. Separate components and dose based on glomerular filtration rate (GFR).

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TABLE C-2 NON-NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS: PREPARATIONS AND DOSING	
Efavirenz, EFV *(Updated November 2008)* (Sustiva)	
Form	50-, 200-mg capsules 600-mg tablets
Dosing Recommendations	Administer on an empty stomach, preferably at bedtime ≥3 y: 10 to <15 kg: 200 mg q24h 15 to <20 kg: 250 mg q24h 20 to <25 kg: 300 mg q24h 25 to <32.5 kg: 350 mg q24h 32.5 to <40 kg: 400 mg q24h ≥40 kg: 600 mg q24h
Adverse Events	*More common:* Skin rash, increased transaminase levels. Central nervous system abnormalities (e.g., somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) primarily reported in adults; symptoms usually subside after 2-4 weeks of therapy.
FDA Pregnancy Category	D (contraindicated during first trimester of pregnancy)
Etravirine, ETR *(Updated November 2009)* (Intelence)	
Form	100-mg tablets
Dosing Recommendations	Safety and effectiveness in pediatric patients have not been established. Adult dose is 200 mg q12h, administered with food, in ARV-experienced patients.
Adverse Events	See Adult *Antiretroviral Therapy* chapter or manufacturer's prescribing information
FDA Pregnancy Category	B
Nevirapine,* NVP *(Updated November 2008)* (Viramune)	
Form	200-mg tablets 10-mg/mL oral solution
Dosing Recommendations	**The 14-day dose escalation lead-in period reduces complications at all ages. Total duration of the once daily lead-in dosing period should not exceed 28 days.** 15 days and older: 150 mg/m^2 q24h for 14 d, then 150 mg/m^2 q12h Calculation based on BSA and 150 mg/m^2 dose: BSA range (m^2) — Volume (mL) 0.06 – 0.12 — 1.25 0.12 – 0.25 — 2.5 0.25 – 0.42 — 5 0.42 – 0.58 — 7.5 0.58 – 0.75 — 10 0.75 – 0.92 — 12.5 0.92 – 1.08 — 15 1.08 – 1.25 — 17.5 1.25+ — 20

	(Younger children [e.g., age ≤8 years] may require a higher dosage [i.e., 200 mg per m^2 of body surface area twice daily, maximum dose 200 mg twice daily]) Max: 200 mg q12h
Adverse Events	*More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. NVP should be permanently discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms, or rash with elevated hepatic transaminases. *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these are less common in children than adults).
FDA Pregnancy Category	C
* Nevirapine should not be used as part of the initial regimen in the following treatment-naïve patients: adolescent and adult females with CD4 counts >250 cells/mm^3, or in adolescent or adult males with CD4 counts >400 cells/mm^3 because of increased incidence of hepatotoxicity.	

TABLE C-3 PROTEASE INHIBITORS: PREPARATIONS AND DOSING	
Atazanavir,[a,b] ATV *(Updated November 2008)* (Reyataz)	
Form	100-, 150-, 200-, 300-mg capsules
Dosing Recommendations	Administer with food. Dosage depends on age, previous ARV experience, and body weight (kg) <3 mo: Not recommended; unknown risks associated with hyperbilirubinemia 3 mo-6 y: Unknown; not currently recommended ≥6 y (and >25 kg) – 21y: 7 mg/kg (or, 200 mg/m^2) ATV + 100 mg RTV q24h (round dosage up to nearest 50 mg capsule size, to Max of 300 mg ATV + 100 mg RTV q24h) (*Note*: An FDA-approved alternative for ARV-naïve adolescents >16y is to give 400 mg q24h without RTV boosting, but clinical trials have shown that the pharmacokinetic parameters with unboosted ATV are unpredictable; the dose may need to be significantly raised above the expected adult maximum. Thus, RTV-boosted dosing as above is preferred. If ATV is administered with either EFV or TDF, the RTV-boosted regimen must be used).
Adverse Events	*More common:* Asymptomatic elevations in indirect bilirubin, jaundice, headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias. *Less common (more severe):* Prolongation of PR interval of electrocardiogram. Abnormalities in AV conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild to moderate, but in rare cases include life-threatening Stevens-Johnson syndrome. Fat redistribution and lipid abnormalities may be less common than with other PIs. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, elevation in serum transaminases, and nephrolithiasis.
FDA Pregnancy Category	B
Darunavir,[b] DRV *(Updated January 2009)* (Prezista)	
Form	75-, 400-, 600-mg tablets
Dosing Recommendations	Must be co-administered with ritonavir; administer with food **For ARV-naïve patients:** 6 to <18 y: use "ARV-experienced" dosing below ≥18 y: 800 mg DRV (two 400-mg tablets) + 100 RTV mg q24h

	For ARV-experienced patients: 6 to < 18 y: ≥20 kg - <30 kg: 375 mg DRV (five 75-mg tabs) + 50 mg RTV (0.6 mL of 80 mg/mL) q12h ≥30 kg - <40 kg: 450 mg DRV (six 75-mg tabs) + 60 mg RTV (0.8 mL of 80 mg/mL) q12h ≥40 kg: 600 mg DRV (one 600-mg tab) + 100 mg RTV (one 100-mg gelcap) q12h ≥18 y: 600 mg DRV + 100 mg RTV q12 *Note:* Pill burden and need for RTV oral solution may complicate adherence in children <40kg.
Adverse Events	*More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue. DRV contains a sulfonamide moiety – Use with caution in patients with severe sulfa allergy. *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome, has been reported. Fever and elevated hepatic transaminases have been reported. Lipid abnormalities. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs. Hepatic dysfunction and acute hepatitis, particularly in patients with underlying risk factors (e.g., hepatitis B or hepatitis C virus co-infection, baseline elevation in transaminases).
FDA Pregnancy Category	C
Fosamprenavir,[b] FPV *(Updated November 2009)* (Lexiva)	
Form	700-mg tablets 50-mg/mL oral suspension
Dosing Recommendations	Dosage depends on age, previous ARV experience, and body weight (kg) Once daily dosing is not recommended for pediatric patients **ARV-naïve, 2-5 y:** 30 mg/kg q12h (Max: 1400 mg q12h) **ARV-naïve, ≥6 y:** 30 mg/kg q12h (Max: 1400 mg q12h) ***or*** 18 mg/kg FPV + 3 mg/kg RTV q12h (Max: 700 mg FPV + 100 mg RTV q12h; may use 2 tablets FPV q12h if ≥47 kg) **ARV-experienced, ≥6 y:** 18 mg/kg FPV + 3 mg/kg RTV q12h (Max: 700 mg FPV + 100 mg RTV q12h; may use 1 tablet FPV with 1 capsule RTV if ≥39 kg) RTV capsules can be used in patients weighing at least 33 kg; patients weighing less should be given RTV oral solution. See prescribing information for dosing in patients with hepatic impairment.

Adverse Events	*More common:* Vomiting, nausea, diarrhea, perioral paresthesias, headache, rash, and lipid abnormalities. FPV contains a sulfonamide moiety; therefore, should be used with caution in patients with severe sulfa allergy *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat redistribution, neutropenia, and elevated serum creatinine kinase levels. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, and elevation in serum transaminases.
FDA Pregnancy Category	C
Indinavir,[b] IDV *(Updated November 2008)* (Crixivan)	
Form	100-, 200-, 333-, 400-mg capsules
Dosing Recommendations	Administer on an empty stomach with adequate hydration (≥48 oz daily fluid in adult) <3 mo: Not approved or recommended; unknown risks associated with hyperbilirubinemia <13 y: Not approved or recommended ≥13 y: 800 mg q8h Adults: With RTV: 800 mg IDV + 200 mg RTV q12h With EFV: 1000 mg IDV q8h + 600 mg EFV q24h
Adverse Events	*More common:* Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritus, and rash. Nephrolithiasis/urolithiasis with IDV crystal deposits: cumulative frequency is higher in children (29%) than adults (12.4%). *Less common (more severe):* Fat redistribution. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).
FDA Pregnancy Category	C
Lopinavir/ritonavir,[b,c] LPV/r *(Updated February 2011)* (Kaletra)	
Form	100/25-, 200/50-mg film-coated tablets 80/20-mg/mL oral solution (contains 42% alcohol and 15% propylene glycol)
Dosing Recommendations	LPV/r liquid must be given with food LPV/r tablets may be given with or without food **Without concurrent NVP, EFV, FPV or NFV:** *Oral solution* 14 d-6 mo:[c] 16 mg per kg LPV/4 mg per kg RTV q12h 6 mo-8 y: <15 kg: 12 mg per kg LPV/3 mg per kg RTV q12h >15 to 40 kg: 10 mg per kg LPV/2.5 mg per kg RTV q12h

	Tablets 6 mo-18 y: 15 to 25 kg: 200 mg LPV/50 mg RTV q12h ≥25 to 35 kg: 300 mg LPV/75 mg RTV q12h ≥35 kg: 400 mg LPV/100 mg RTV q12h >18 y: 400 mg LPV/100 mg RTV q12h (For patients who are >18 y, treatment-naïve, and who have HIV RNA <100,000 copies/mL, some experts suggest 800 mg LPV/200 mg RTV q24h) **With concurrent NVP, EFV, FPV, or NFV (dose scaled up because of induction of LPV metabolism):** *Oral solution* 6 mo – 18 y: <15 kg: 13 mg per kg LPV/3.25 mg per kg RTV q12h >15 to 40 kg: 11 mg per kg LPV/2.7 mg per kg RTV q12h *Tablets* 6 mo-18 y: 15 to 20 kg: 200 mg LPV/50 mg RTV q12h ≥20 to 30 kg: 300 mg LPV/75 mg RTV q12h ≥30 to 45 kg: 400 mg LPV/100 mg RTV q12h ≥45 kg: 400 mg LPV/100 mg RTV q12h ***or*** ≥45 kg: 600 mg LPV/150 mg RTV q12h
Adverse Events	*More common:* Diarrhea, headache, asthenia, nausea and vomiting, and rash in patients receiving LPV/RTV with other antiretroviral drugs; lipid abnormalities. *Less common (more severe):* Fat redistribution. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, and hepatitis (life-threatening in rare cases).
FDA Pregnancy Category	C
	Nelfinavir, NFV *(Updated November 2008)* (Viracept)
Form	50 mg per 1 level gram scoopful powder for oral solution 250-, 625-mg tablets
Dosing Recommendations	>2-13 y: 45-55 mg/kg q12h ***or*** 20-35 mg/kg tid (Max: 2500 mg per day) ≥13 y: 1250 mg q12h or 750 mg tid
Adverse Events	*More common:* Diarrhea (most common). Asthenia, abdominal pain, rash, and lipid abnormalities. *Less common (more severe):* Exacerbation of chronic liver disease. Fat redistribution. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases.
FDA Pregnancy Category	B

Ritonavir,[d] RTV *(Updated November 2008)* (Norvir)	
Form	80-mg/mL oral solution 100-mg gel capsules
Dosing Recommendations	Most commonly used as a PK booster at 100 mg q12h For other boosting regimens and full dosing recommendations, refer to Adult *Antiretroviral Therapy* chapter and the federal *Pediatric Antiretroviral Guidelines*
Adverse Events	*More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesias, lipid abnormalities. *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema.
FDA Pregnancy Category	B
Saquinavir,[b] SQV *(Updated November 2008)* (Invirase; soft-gel capsule Fortovase discontinued)	
Form	200-mg hard gel capsules 500-mg film coated tablets
Dosing Recommendations	Must be boosted with ritonavir >16 y: 1000 mg SQV + 100 mg RTV q12h (administered with food)
Adverse Events	*More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesias, skin rash, and lipid abnormalities. *Less common (more severe):* Exacerbation of chronic liver disease, fat redistribution. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis, and elevation in serum transaminases.
FDA Pregnancy Category	B
Tipranavir,[b] TPV *(Updated November 2008)* (Aptivus)	
Form	250-mg capsules 100 mg/mL oral solution
Dosing Recommendations	Must be boosted with ritonavir; may be better tolerated when administered with food. Oral solution (but not capsules) contains 116 IU vitamin E per mL; do not give with vitamin E-containing supplements. ≥2-18 y: 14 mg per kg TPV/6 mg per kg RTV q12h Max: 500 mg TRV + 200 mg RTV q12h >18 y: 500 mg TPV + 200 mg RTV q12h
Adverse Events	*More common:* Diarrhea, nausea, fatigue, headache, rash (more frequent in children than adults), and vomiting. Laboratory abnormalities are elevated liver enzymes, cholesterol, and triglycerides. TPV contains a sulfonamide moiety; therefore, should be used with caution in patients with severe sulfa allergy.

	Less common (more severe): Fat redistribution. Clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or C co-infection or elevations in transaminases are at increased risk for developing further transaminase elevations or hepatic decompensation (approximately 2.5-fold risk). Epistaxis. Rarely, new onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs. Possible association with increased risk of intracranial hemorrhage.
FDA Pregnancy Category	C

[a] When given in combination with efavirenz or tenofovir, atazanavir must be given with ritonavir-boosting. To avoid reduction of atazanavir absorption, atazanavir should be given 2 hours before or 1 hour after didanosine.

[b] Saquinavir, darunavir, and tipranavir must be given with ritonavir. Indinavir, atazanavir, and, to a lesser-degree, fosamprenavir are generally given with ritonavir-boosting to enhance pharmacokinetics and allow lower and less frequent dosing. Lopinavir is already coformulated with ritonavir.

[c] Dosing should be based on the mg/kg recommendations in the manufacturer's tables for each individual child. LPV/r oral solution should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained, because of reports of cardiac toxicity (which may be fatal), lactic acidosis, acute renal failure, central nervous system depression, and respiratory complications in preterm newborns. Consultation with a pediatric provider who has extensive experience with HIV management is advised.

[d] Consult with a pediatric provider who has extensive experience with HIV management when dosing with ritonavir alone.

[e] Tipranavir should not be used in patients with moderate to severe hepatic insufficiency.

TABLE C-4 FUSION INHIBITORS: PREPARATIONS AND DOSING	
Enfuvirtide, T20 *(Updated November 2008)* (Fuzeon)	
Form	Injectable lyophylized powder; each single-use vial contains 108 mg of T-20 to be reconstituted with 1.1 mL of sterile water for injection of approximately 90 mg/1 mL
Dosing Recommendations	<6 y: Not approved 6-16 y: 2 mg/kg/dose SC injection q12h into the upper arm, anterior thigh, or abdomen* Suggested volumes per dose by BW: 11-15.5 kg: 0.3 mL (27 mg) 15.6-20 kg: 0.4 mL (36 mg) 20.1-24.5 kg: 0.5 mL (45 mg) 24.6-29 kg: 0.6 mL (54 mg) 29.1-33.5 kg: 0.7 mL (63 mg) 33.6-38 kg: 0.8 mL (72 mg) 38.1-42.5 kg: 0.9 mL (81 mg) >42.5 kg: 1.0 mL (90 mg) >16 y: 90 mg (1.0 mL)
Adverse Events	*Most common:* Almost all patients (87%–98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients. *Less common*: Increased rate of bacterial pneumonia (unclear association) and local site cellulitis (3%-8%). Rarely, hypersensitivity reactions (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barré syndrome. Patients experiencing hypersensitivity reactions should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with hypersensitivity reactions.
FDA Pregnancy Category	B
* For all dosing, SC q12h into the upper arm, anterior thigh, or abdomen at a site different from the preceding injection site, and only where no current injection site reaction exists. Do not inject where large nerves course close to skin, over a blood vessel, into moles, scar tissue, tattoos, burn sites, or around the navel.	

TABLE C-5 CCR5 CO-RECEPTOR ANTAGONISTS: PREPARATIONS AND DOSING	
Maraviroc,* MVC *(Updated December 2008)* (Selzentry)	
Form	150-, 300-mg tablets
Dosing Recommendations	Data not available in pediatric patients, and not approved for use in patients <16 years of age. Adult dose is dependent on concurrent usage of CYP3A4 inhibitors or inducers, and ranges between 150 to 600 mg q12h (for regimens and full dosing recommendations, refer to Adult *Antiretroviral Therapy* chapter and the federal *Pediatric Antiretroviral Guidelines).*
Adverse Events	*More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness. *Less common (more severe):* Serious adverse events occurred in less than 2% of MVC-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.
FDA Pregnancy Category	B
* A viral tropism assay (Trofile, Monogram Biosciences) is required before initiating therapy with maraviroc (only CCR5-tropic HIV is expected to be susceptible).	

TABLE C-6 INTEGRASE INHIBITORS PREPARATIONS AND DOSING	
Raltegravir, RAL *(Updated November 2008)* (Isentress)	
Form	400-mg film-coated tablets
Dosing Recommendations	Data not available in pediatric patients, and not approved for use in patients <16 years Adult dose, 400 mg twice daily
Adverse Events	*More common:* Nausea, headache, dizziness, diarrhea, fatigue, and itching. *Less common:* Abdominal pain, vomiting. In patients co-infected with chronic active hepatitis B and/or C, worsening of laboratory abnormalities from baseline AST, ALT, or total bilirubin more likely than in patients not co-infected. Rarely, creatine kinase elevations (grade 2-4) have been observed in some patients. Myopathy and rhabdomyolysis have been reported. Caution is advised in patients receiving medications associated with these toxicities.
FDA Pregnancy Category	C