Tables from the

Guidelines for the Use of Antiretroviral Agents in Pediatric Infection

August 16, 2010

This document includes all the tables and figures found in the main body of the August 16, 2010, HHS Guidelines for the Use of Antiretroviral Agents in Pediatric Infection. The tables and figures are identical in numbering and content to those found in the main guidelines document. References that may accompany the tables within the main document are not included here; please refer to the full document.

Drug tables from Appendix B: Pediatric Antiretroviral Drug Information are included in a separate tables document.
children, adolescents, and adults and, when no definitive data were available, the clinical expertise of the Panel members. The Panel intends the guidelines to be flexible and not to replace the clinical judgment of experienced health care providers.

GUIDELINES DEVELOPMENT PROCESS

An outline of the composition of the Panel and the guidelines process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process

<table>
<thead>
<tr>
<th>Topic</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal of the Guidelines</td>
<td>Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents in HIV-1-infected infants, children, and adolescents (through puberty) in the United States.</td>
</tr>
<tr>
<td>Panel members</td>
<td>The Panel is composed of approximately 25 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection. The Panel also includes at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found on page viii of this document.</td>
</tr>
<tr>
<td>Financial disclosure</td>
<td>All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in Appendix A of this document.</td>
</tr>
<tr>
<td>Users of the guidelines</td>
<td>Providers of care to HIV-infected infants, children, and adolescents</td>
</tr>
<tr>
<td>Funding source</td>
<td>Office of AIDS Research, NIH</td>
</tr>
<tr>
<td>Evidence collection</td>
<td>The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.</td>
</tr>
<tr>
<td>Recommendation grading</td>
<td>As described in Table 2.</td>
</tr>
<tr>
<td>Method of synthesizing data</td>
<td>Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.</td>
</tr>
</tbody>
</table>

Guidelines for the Use of Antiretroviral Agents in Pediatric Infection
Other guidelines
These guidelines focus on HIV-infected infants, children, and adolescents through puberty. Separate guidelines outline the use of antiretroviral therapy in pregnant HIV-infected women and interventions for prevention of mother-to-child transmission, antiretroviral therapy for nonpregnant HIV-infected adults and postpubertal adolescents, and antiretroviral prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the AIDSinfo Web site (http://www.aidsinfo.nih.gov).

These guidelines focus on HIV-infected children from infancy through puberty. For more detailed discussion on issues of treatment of postpubertal adolescents, the Panel defers to the designated expertise offered by the Panel on Antiretroviral Guidelines for Adults and Adolescents.

Update plan
The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel’s recommendations may be made on the AIDSinfo Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the AIDSinfo Web site (http://www.aidsinfo.nih.gov).

Public comments
A 2-week public comment period follows release of the updated guidelines on the AIDSinfo Web site. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Basis for Recommendations
Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommendation includes a letter (A, B, or C) that represents the strength of the recommendation and a Roman numeral (I, II, or III) that represents the quality of the evidence that supports the recommendation.

Because licensure of drugs in children often relies on efficacy data from adult trials in addition to safety and pharmacokinetic data in children, recommendations for antiretroviral drugs may need to rely on data from clinical trials or studies in adults. Pediatric drug approval may be based on evidence from adequate and well-controlled investigations in adults if:

1. it is expected that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation of adult efficacy data to pediatric patients;
2. there are supplemental data on pharmacokinetics of the drug in children so that systemic exposure in adults and children are similar; and
3. studies supporting the safety of the drug in pediatric patients are provided [10].

In addition, if there was a concern that concentration-response relationships may be different in children, studies relating activity of the drug-to-drug levels (pharmacodynamic data) in children should be available.
Table 2. Rating Scheme for Recommendations

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials in children† with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>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</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>II: One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term clinical outcomes</td>
</tr>
<tr>
<td></td>
<td>II*: One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes with accompanying data in children† from one or more smaller nonrandomized trials or cohort studies with clinical outcome data</td>
</tr>
<tr>
<td></td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

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

CONCEPTS CONSIDERED IN THE FORMULATION OF PEDIATRIC TREATMENT GUIDELINES

The following concepts were considered in the formulation of these guidelines.

• Prenatal HIV testing and counseling should be the standard of care for all pregnant women in the United States [11-13]. Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their infants and for reduction of perinatal transmission. Access to prenatal care is essential for all pregnant women.

• Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.*

• The pharmaceutical industry and the federal government should continue collaboration that assures that drug formulations suitable for administration to infants and children are available for all antiretroviral drugs produced.

• Although some information regarding the efficacy of antiretroviral drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of Phase III efficacy trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children.

* In areas where enrollment in clinical trials is possible, enrolling the child in available trials should be discussed with the caregivers of the child. Information about clinical trials for HIV-infected adults and children can be obtained from the AIDSinfo Web site (http://aidsinfo.nih.gov/ClinicalTrials/) or by telephone at 1-800-448-0440.
Table 3. Likelihood of Developing AIDS or Death Within 12 Months, by Age and CD4⁺ T-Cell Percentage or Log₁₀ HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

<table>
<thead>
<tr>
<th>Age</th>
<th>CD4 Percentage</th>
<th>Log₁₀ HIV RNA Copy Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10%  20%  25%  30%</td>
<td>6.0  5.0  4.0</td>
</tr>
<tr>
<td>Percent Mortality (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>28.7  12.4  8.5  6.4</td>
<td>9.7  4.1  2.7</td>
</tr>
<tr>
<td>1 Year</td>
<td>19.5  6.8  4.5  3.3</td>
<td>8.8  3.1  1.7</td>
</tr>
<tr>
<td>2 Years</td>
<td>11.7  3.1  2.0  1.5</td>
<td>8.2  2.5  1.1</td>
</tr>
<tr>
<td>5 Years</td>
<td>4.9   0.9  0.6  0.5</td>
<td>7.8  2.1  0.7</td>
</tr>
<tr>
<td>10 Years</td>
<td>2.1   0.3  0.2  0.2</td>
<td>7.7  2.0  0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent Developing AIDS (95% Confidence Interval)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>51.4  31.2  24.9  20.5</td>
<td>23.7  13.6  10.9</td>
</tr>
<tr>
<td>1 Year</td>
<td>40.5  20.9  15.9  12.8</td>
<td>20.9  10.5  7.8</td>
</tr>
<tr>
<td>2 Years</td>
<td>28.6  12.0  8.8  7.2</td>
<td>18.8  8.1  5.3</td>
</tr>
<tr>
<td>5 Years</td>
<td>14.7  4.7  3.7  3.1</td>
<td>17.0  6.0  3.2</td>
</tr>
<tr>
<td>10 Years</td>
<td>7.4   2.2  1.9  1.8</td>
<td>16.2  5.1  2.2</td>
</tr>
</tbody>
</table>

Table 4. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)*

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Absolute CD4 cell count (cells/mm³)</th>
<th>&lt;50</th>
<th>50–99</th>
<th>100–199</th>
<th>200–349</th>
<th>350–499</th>
<th>500+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of Death Per 100 Patient-Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>59.3</td>
<td>39.6</td>
<td>25.4</td>
<td>11.1</td>
<td>10.0</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>5–14</td>
<td>28.9</td>
<td>11.8</td>
<td>4.3</td>
<td>0.89</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>34.7</td>
<td>6.1</td>
<td>1.1</td>
<td>0.71</td>
<td>0.58</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>25–34</td>
<td>47.7</td>
<td>10.8</td>
<td>3.7</td>
<td>1.1</td>
<td>0.38</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>58.8</td>
<td>15.6</td>
<td>4.5</td>
<td>0.92</td>
<td>0.74</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>66.0</td>
<td>18.8</td>
<td>7.7</td>
<td>1.8</td>
<td>1.3</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>55+</td>
<td>91.3</td>
<td>21.4</td>
<td>17.6</td>
<td>3.8</td>
<td>2.5</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Rate of AIDS or Death per 100 Patient-Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>82.4</td>
<td>83.2</td>
<td>57.3</td>
<td>21.4</td>
<td>20.7</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>5–14</td>
<td>64.3</td>
<td>19.6</td>
<td>16.0</td>
<td>6.1</td>
<td>4.4</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>61.7</td>
<td>30.2</td>
<td>5.9</td>
<td>2.6</td>
<td>1.8</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>25–34</td>
<td>93.2</td>
<td>57.6</td>
<td>19.3</td>
<td>6.1</td>
<td>2.3</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>88.1</td>
<td>58.7</td>
<td>25.5</td>
<td>6.6</td>
<td>4.0</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>45–54</td>
<td>129.1</td>
<td>56.2</td>
<td>24.7</td>
<td>7.7</td>
<td>3.1</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>55+</td>
<td>157.9</td>
<td>42.5</td>
<td>30.0</td>
<td>10.0</td>
<td>5.1</td>
<td>1.8</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4⁺ T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children

<table>
<thead>
<tr>
<th>Baseline HIV RNA \ (copies/mL)/Baseline CD4⁺ T-cell percentage</th>
<th>No. patients \ (patients)</th>
<th>No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 100,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 15%</td>
<td>103</td>
<td>15</td>
<td>(15%)</td>
</tr>
<tr>
<td>&lt; 15%</td>
<td>24</td>
<td>15</td>
<td>(63%)</td>
</tr>
<tr>
<td>&gt; 100,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 15%</td>
<td>89</td>
<td>32</td>
<td>(36%)</td>
</tr>
<tr>
<td>&lt; 15%</td>
<td>36</td>
<td>29</td>
<td>(81%)</td>
</tr>
</tbody>
</table>

* Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.
† Mean follow-up: 5.1 years.
§ Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.
¶ Mean age: 3.4 years.

Figure 1. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy [modified from Lancet 2003;362:1605-11]

Figure 2. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy [modified from Lancet 2003;362:1605-11]
Figure 3. Death Rate per 100 Person-Years in HIV-Infected Children Age 5 years or Older in the HIV Pediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study*

Figure 4. Estimated Probability of AIDS Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy [modified from Lancet 2003;362:1605-11]

Figure 5. Estimated Probability of Death Within 12 Months by Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy [modified from Lancet 2003;362:1605-11]
### Table 6. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical Categories*

<table>
<thead>
<tr>
<th>Category N: Not Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category A: Mildly Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with two or more of the following conditions but none of the conditions listed in Categories B and C:</td>
</tr>
<tr>
<td>• Lymphadenopathy (≥0.5 cm at more than two sites; bilateral = one site)</td>
</tr>
<tr>
<td>• Hepatomegaly</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Dermatitis</td>
</tr>
<tr>
<td>• Parotitis</td>
</tr>
<tr>
<td>• Recurrent or persistent upper respiratory infection, sinusitis, or otitis media</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category B: Moderately Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children who have symptomatic conditions, other than those listed for Category A or Category C, that are attributed to HIV infection. Examples of conditions in Clinical Category B include, but are not limited to, the following:</td>
</tr>
<tr>
<td>• Anemia (&lt;8 gm/dL), neutropenia (&lt;1,000 cells/mm³), or thrombocytopenia (&lt;100,000 cells/mm³) persisting ≥30 days</td>
</tr>
<tr>
<td>• Bacterial meningitis, pneumonia, or sepsis (single episode)</td>
</tr>
<tr>
<td>• Candidiasis, oropharyngeal (i.e., thrush) persisting for &gt;2 months in children age &gt;6 months</td>
</tr>
<tr>
<td>• Cardiomyopathy</td>
</tr>
<tr>
<td>• Cytomegalovirus infection with onset before age 1 month</td>
</tr>
<tr>
<td>• Diarrhea, recurrent or chronic</td>
</tr>
<tr>
<td>• Hepatitis</td>
</tr>
<tr>
<td>• Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)</td>
</tr>
<tr>
<td>• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month</td>
</tr>
<tr>
<td>• Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome</td>
</tr>
<tr>
<td>• Leiomyosarcoma</td>
</tr>
<tr>
<td>• Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex</td>
</tr>
<tr>
<td>• Nephropathy</td>
</tr>
<tr>
<td>• Nocardiosis</td>
</tr>
<tr>
<td>• Fever lasting &gt;1 month</td>
</tr>
<tr>
<td>• Toxoplasmosis with onset before age 1 month</td>
</tr>
<tr>
<td>• Varicella, disseminated (i.e., complicated chickenpox)</td>
</tr>
</tbody>
</table>
### Category C: Severely Symptomatic

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

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
- Cytomegalovirus disease with onset of symptoms at age >1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for >1 month or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium complex or Mycobacterium kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jiroveci* pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at >1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss >10% of baseline; OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥1 year of age; OR c) <5th percentile on weight-for-height chart on two consecutive measurements, ≥30 days apart **PLUS** 1) chronic diarrhea (i.e., ≥ two loose stools per day for >30 days), **OR** 2) documented fever (for ≥30 days, intermittent or constant)

**Table 7. Indications for Initiation of Antiretroviral Therapy in HIV-Infected Children**

This table provides general guidance rather than absolute recommendations for an individual patient. Factors to be considered in decisions about initiation of therapy include the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number, the potential benefits and risks of therapy, and the ability of the caregiver to adhere to administration of the therapeutic regimen. Issues associated with adherence should be fully assessed, discussed, and addressed with the child, if age appropriate, and the caregiver before the decision to initiate therapy is made.

<table>
<thead>
<tr>
<th>Age</th>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 months</td>
<td>• Regardless of clinical symptoms, immune status, or viral load</td>
<td>Treat (AI)</td>
</tr>
<tr>
<td>1--&lt;5 years</td>
<td>• AIDS or significant HIV-related symptoms(^1)</td>
<td>Treat (AI*)</td>
</tr>
<tr>
<td></td>
<td>• CD4 &lt;25%, regardless of symptoms or HIV RNA level</td>
<td>Treat (AII)</td>
</tr>
<tr>
<td></td>
<td>• Asymptomatic or mild symptoms(^2) and</td>
<td>Treat (BII)</td>
</tr>
<tr>
<td></td>
<td>• CD4 ≥25% \and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• HIV RNA ≥100,000 copies/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Asymptomatic or mild symptoms(^2) and</td>
<td>Consider or Defer(^3)</td>
</tr>
<tr>
<td></td>
<td>• CD4 ≥25% \and</td>
<td>(CIII)</td>
</tr>
<tr>
<td></td>
<td>• HIV RNA &lt;100,000 copies/mL</td>
<td></td>
</tr>
<tr>
<td>≥5 years</td>
<td>• AIDS or significant HIV-related symptoms(^1)</td>
<td>Treat (AI*)</td>
</tr>
<tr>
<td></td>
<td>• CD4 &lt;350 cells/mm(^3)</td>
<td>Treat (AI*)</td>
</tr>
<tr>
<td></td>
<td>• Asymptomatic or mild symptoms(^2) and</td>
<td>Treat (BII)</td>
</tr>
<tr>
<td></td>
<td>• CD4 ≥350 cells/mm(^3) \and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• HIV RNA ≥100,000 copies/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Asymptomatic or mild symptoms(^2) and</td>
<td>Consider or Defer(^3)</td>
</tr>
<tr>
<td></td>
<td>• CD4 ≥350 cells/mm(^3) \and</td>
<td>(CIII)</td>
</tr>
<tr>
<td></td>
<td>• HIV RNA &lt;100,000 copies/mL</td>
<td></td>
</tr>
</tbody>
</table>

---

1  CDC Clinical Categories C and B (except for the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis)

2  CDC Clinical Category A or N or the following Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis

3  Clinical and laboratory data should be re-evaluated every 3 to 4 months.
A combination antiretroviral regimen in treatment-naïve children generally contains 1 NNRTI plus a 2-NRTI backbone or 1 PI plus a 2-NRTI backbone. A 3-NRTI regimen consisting of zidovudine, abacavir, and lamivudine is recommended only if a PI or NNRTI regimen cannot be used. Regimens should be individualized based on advantages and disadvantages of each combination (see Tables 11–13).

### Preferred Regimens

| Children <3 years of age: | Two NRTIs plus lopinavir/ritonavir³ |
| Children ≥3 years of age: | Two NRTIs plus nevirapine¹,₃ (only if no peripartum nevirapine exposure) |

### Alternative Regimens

| Children <3 years of age: | None |
| Children ≥3 to <6 years of age: | Two NRTIs plus nevirapine¹,₃ |
| Children ≥6 years of age | Two NRTIs plus atazanavir plus low-dose ritonavir |

### Use in Special Circumstances

| Two NRTIs plus atazanavir unboosted (for treatment-naïve adolescents ≥13 years of age and >39 kg) |
| Two NRTIs plus fosamprenavir unboosted (children ≥2 years of age) |
| Two NRTIs plus nelfinavir (children ≥2 years of age) |
| Zidovudine plus lamivudine plus abacavir |

### 2-NRTI Backbone Options (for use in combination with additional drugs) (alphabetical ordering)

| Preferred | Abacavir plus (lamivudine or emtricitabine) |
| Alternative | Zidovudine plus abacavir |
| Use in Special Circumstances | Stavudine plus (lamivudine or emtricitabine) |
Not Recommended for Initial Therapy

- Etravirine-containing regimens
- Efavirenz-containing regimens for children <3 years of age
- Tipranavir-containing regimens
- Saquinavir-containing regimens
- Indinavir-containing regimens
- Dual (full-dose) PI regimens
- Full-dose ritonavir or use of ritonavir as the sole PI
- Unboosted atazanavir-containing regimens in children <13 years of age and/or <39 kg
- Nelfinavir-containing regimens for children <2 years old
- Unboosted darunavir regimens using once-daily dosing of lopinavir/ritonavir, boosted darunavir, or fosamprenavir (boosted or unboosted)
- Triple-NRTI regimens other than abacavir + zidovudine + lamivudine
- Triple-class regimens, including NRTI plus NNRTI plus PI
- Regimens with dual-NRTI backbones of abacavir + didanosine, abacavir + tenofovir, didanosine + tenofovir, and didanosine + stavudine
- Tenofovir-containing regimens in children in Tanner stages 1–3
- Maraviroc-containing regimens
- Raltegravir-containing regimens
- Enfuvirtide (T-20)-containing regimens

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1 Efavirenz is currently available only in capsule form and should be used only in children ≥3 years of age with weight ≥10 kg; nevirapine would be the preferred NNRTI for children age <3 years of age (excluding infants who were exposed to nevirapine as part of maternal-infant peripartum prophylaxis) or who require a liquid formulation. Unless adequate contraception can be ensured, efavirenz-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

2 With the exception of lopinavir/ritonavir at all ages and atazanavir/ritonavir, fosamprenavir/ritonavir, and darunavir/ritonavir in children ≥6 years of age, use of other boosted PIs as a component of initial therapy is not recommended, although such regimens have utility as secondary treatment regimens for children who have failed initial therapy.

3 For children <3 years of age, nevirapine is the preferred NNRTI when NNRTI-based therapy is used. However, lopinavir/ritonavir is preferred to nevirapine by many experts. Nevirapine should not be used in infants who have been exposed to nevirapine as part of maternal-infant prophylaxis.

4 Nevirapine should not be used in postpubertal girls with CD4 count >250/mm³, unless the benefit clearly outweighs the risk.
### Table 9. Antiretroviral Regimens or Components that Should Never Be Offered for Treatment of Human Immunodeficiency Virus (HIV) Infection in Children

<table>
<thead>
<tr>
<th>Antiretroviral regimens</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td>Rapid development of resistance</td>
<td>HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission</td>
</tr>
<tr>
<td></td>
<td>Inferior antiviral activity compared with combination with ≥3 antiretroviral drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Two NRTIs alone</strong></td>
<td>Rapid development of resistance</td>
<td>Not recommended for initial therapy; for patients currently on this treatment, some clinicians may opt to continue if virologic goals are achieved</td>
</tr>
<tr>
<td></td>
<td>Inferior antiviral activity compared with combination with ≥3 antiretroviral drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Tenofovir plus abacavir</strong></td>
<td>High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naïve adults</td>
<td>No exception</td>
</tr>
<tr>
<td><strong>plus lamivudine or emtricitabine as a triple-NRTI regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tenofovir plus didanosine</strong></td>
<td>High rate of early viral failure when this triple-NRTI regimen used as initial therapy in treatment-naïve adults</td>
<td>No exception</td>
</tr>
<tr>
<td><strong>plus lamivudine or emtricitabine as a triple-NRTI regimen</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiretroviral components</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atazanavir plus indinavir</strong></td>
<td>Potential additive hyperbilirubinemia</td>
<td>No exception</td>
</tr>
<tr>
<td><strong>Dual-NRTI combinations</strong></td>
<td>Enhanced toxicity</td>
<td>No exception</td>
</tr>
<tr>
<td><strong>Dual-NRTI combinations:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine plus emtricitabine</td>
<td>Similar resistance profile and no additive benefit</td>
<td>No exception</td>
</tr>
<tr>
<td>Stavudine plus zidovudine</td>
<td>Antagonistic effect on HIV</td>
<td>No exception</td>
</tr>
<tr>
<td><strong>Efavirenz in first trimester of pregnancy or for sexually active adolescent girls of childbearing potential when reliable contraception cannot be ensured</strong></td>
<td>Potential for teratogenicity</td>
<td>When no other antiretroviral option is available and potential benefits outweigh risks</td>
</tr>
<tr>
<td><strong>Nevirapine initiation in adolescent girls with CD4 &gt;250 cells/mm³ or adolescent boys with CD4 &gt;400 cells/mm³</strong></td>
<td>Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups</td>
<td>Only if benefit clearly outweighs the risk</td>
</tr>
<tr>
<td><strong>Unboosted saquinavir, darunavir, or tipranavir</strong></td>
<td>Poor oral bioavailability</td>
<td>No exception</td>
</tr>
<tr>
<td><strong>Inferior virologic activity compared with other protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

<table>
<thead>
<tr>
<th>Preferred Combinations</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Abacavir plus lamivudine or emtricitabine | • Palatable liquid formulations  
  • Can give with food  
  • Abacavir and lamivudine are coformulated as a single pill for older/larger patients | • Risk of abacavir hypersensitivity reaction; perform HLA-B*5701 screening prior to initiation of abacavir treatment |
| Didanosine plus lamivudine or emtricitabine | • Delayed-release capsules of didanosine may allow once-daily dosing in older children able to swallow pills and who can receive adult dosing along with once-daily emtricitabine  
  • Emtricitabine available as a palatable liquid formulation administered once daily | • Food effect (didanosine is recommended to be taken 1 hour before or 2 hours after food) – some experts give didanosine without regard to food in infants or when compliance is an issue (but can be coadministered with emtricitabine or lamivudine)  
  • Limited pediatric experience using delayed-release didanosine capsules in younger children  
  • Pancreatitis, neurotoxicity with didanosine |
| Zidovudine plus lamivudine or emtricitabine | • Extensive pediatric experience  
  • Zidovudine and lamivudine are coformulated as single pill for older/larger patients  
  • Palatable liquid formulations  
  • Can give with food  
  • Emtricitabine available as a palatable liquid formulation administered once daily | • Bone marrow suppression with zidovudine  
  • Lipodystrophy with zidovudine |
| Tenofovir plus lamivudine or emtricitabine for Tanner stage 4 or postpubertal adolescents only | • Resistance slow to develop  
  • Once-daily dosing for tenofovir  
  • Less mitochondrial toxicity than other NRTIs  
  • Can give with food  
  • Bone toxicity may be less in postpubertal children  
  • Tenofovir and emtricitabine are coformulated as single pill for older/larger patients | • No pediatric formulation of tenofovir  
  • Limited pediatric experience  
  • Potential bone and renal toxicity  
  • Numerous drug-drug interactions with other ARV agents including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir complicate appropriate dosing |

<table>
<thead>
<tr>
<th>Alternate Combinations</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Zidovudine plus abacavir | • Palatable liquid formulations  
  • Can give with food | • Risk of abacavir hypersensitivity reaction; perform HLA-B*5701 screening prior to initiation of abacavir treatment  
  • Bone marrow suppression and lipodystrophy with zidovudine |
| Zidovudine plus didanosine | • Extensive pediatric experience  
  • Delayed-release capsules of didanosine may allow once-daily dosing of didanosine in older children able to swallow pills and who can receive adult dosing | • Bone marrow suppression and lipodystrophy with zidovudine  
  • Pancreatitis, neurotoxicity with didanosine  
  • Didanosine liquid formulation less palatable than lamivudine or emtricitabine liquid formulation  
  • Food effect (recommended to take didanosine 1 hour before or 2 hours after food); some experts give didanosine without regard to food in infants or when compliance is an issue |
Table 10: Advantages and Disadvantages of Different Nucleoside or Nucleotide Analogue Reverse Transcriptase Inhibitor (NRTI, NtRTI) Backbone Combinations for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

<table>
<thead>
<tr>
<th>Use in Special Circumstances</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Stavudine** *plus* lamivudine or emtricitabine | • Moderate pediatric experience  
• Palatable liquid formulations  
• Can give with food  
• Emtricitabine available as a palatable liquid formulation administered once daily | • Stavudine associated with higher incidence of hyperlactatemia/lactic acidosis, lipoatrophy, peripheral neuropathy, hyperlipidemia  
• Limited pediatric experience with stavudine plus emtricitabine |

<table>
<thead>
<tr>
<th>Not Recommended</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Tenofovir-containing regimens** in children in Tanner stages 1–3 | • Resistance slow to develop  
• Once-daily dosing for tenofovir (adults)  
• Less mitochondrial toxicity than other NRTIs  
• Can give with food | • No pediatric formulation of tenofovir  
• **Limited PK data for tenofovir in children**  
• Limited pediatric experience  
• Potential bone and renal toxicity; bone toxicity appears to be more frequent in younger children  
• Numerous drug-drug interactions with other ARV agents including didanosine, lopinavir/ritonavir, atazanavir, and tipranavir complicate appropriate dosing |

| Zidovudine *plus* stavudine | • None | Pharmacologic and antiviral antagonism |
| Lamivudine *plus* emtricitabine | • None | Similar drug structure  
• Single mutation (M184V) associated with resistance to both drugs |
| Stavudine *plus* Didanosine | • Has shown antiviral activity in small studies in children  
• Although not recommended for initial therapy, it may be considered for use in antiretroviral-experienced children who require a change in therapy | Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis |
Table 11. Advantages and Disadvantages of Different Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

<table>
<thead>
<tr>
<th>General Issues</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI-Based Regimens</strong></td>
<td><strong>NNRTI Class Advantages:</strong></td>
<td><strong>NNRTI Class Disadvantages:</strong></td>
</tr>
<tr>
<td></td>
<td>• Less dyslipidemia and fat maldistribution than protease inhibitors</td>
<td>• Single mutation can confer resistance, with cross resistance between efavirenz and nevirapine</td>
</tr>
<tr>
<td></td>
<td>• Protease inhibitor sparing</td>
<td>• Rare but serious and potentially life-threatening cases of skin rash, including Stevens-Johnson syndrome, and hepatic toxicity with all NNRTIs (but highest with nevirapine)</td>
</tr>
<tr>
<td></td>
<td>• Lower pill burden than protease inhibitors for those taking solid formulation; easier to use and adhere to than protease inhibitor-based regimens</td>
<td>• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)</td>
</tr>
</tbody>
</table>

<p>| Preferred | | |
| Efavirenz (for children ≥3 years of age and who can take capsules) | • Potent antiretroviral activity | • Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects) |
| | • Once-daily administration | • Rash (generally mild) |
| | • Can give with food (but avoid high fat meals) | • No commercially available liquid |
| Nevirapine for children age &lt;3 years who have not been exposed to nevirapine as part of maternal-infant prophylaxis or who require a liquid formulation | • Liquid formulation available | • No data on dosing for children age &lt;3 years |
| | • Dosing information for young infants available | • Teratogenic in primates; use with caution in adolescent females of childbearing age |
| | • Can give with food | |
| Alternative | | |
| Nevirapine (for children age ≥3 years) | • Liquid formulation available | • Higher incidence of rash/hypersensitivity reaction than other NNRTIs |
| | • Dosing information for young infants available | • Higher rates of serious hepatic toxicity than efavirenz |
| | • Can give with food | • Decreased virologic response compared with efavirenz |
| | | • Need to initiate therapy with a lower dose and increase in a stepwise fashion. This is to allow for auto-induction of nevirapine metabolism and is associated with a lower incidence of toxicity. |
| | | • Twice-daily dosing |</p>
<table>
<thead>
<tr>
<th>Not Recommended</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Efavirenz (for children age <3 years)** | *Potent antiretroviral activity*  
*Once-daily administration*  
*Can give with food (but avoid high fat meals)* | *Neuropsychiatric side effects (bedtime dosing to reduce central nervous system effects)*  
*Rash (generally mild)*  
*No commercially available liquid*  
*No data on dosing for children age <3 years*  
*Teraogenic in primates; use with caution in adolescent females of childbearing age* |
| **Etravirine** | *Three or more baseline NNRTI mutations result in a decreased virologic response*  
*Patients with a history of NNRTI-related rash do not appear to be at increased risk of etravirine-related rash* | *Limited data on pediatric dosing or safety*  
*No pediatric formulation available*  
*Food effect (should be given with food)*  
*No data in treatment-naïve patients*  
*Multiple drug interactions with PIs and other medications*  
*Twice-daily dosing*  
*Skin rash* |
### Table 12. Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

<table>
<thead>
<tr>
<th>General Issues</th>
<th>Protease Class Advantages:</th>
<th>Protease Class Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitor-Based Regimens</td>
<td>- NNRTI sparing</td>
<td>- Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance</td>
</tr>
<tr>
<td></td>
<td>- Clinical, virologic, and immunologic efficacy well documented</td>
<td>- Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)</td>
</tr>
<tr>
<td></td>
<td>- Resistance to protease inhibitors requires multiple mutations</td>
<td>- Higher pill burden than NRTI- or NNRTI-based regimens for those taking solid formulations</td>
</tr>
<tr>
<td></td>
<td>- Targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes)</td>
<td>- Poor palatability of liquid preparations, which may affect adherence to treatment regimen</td>
</tr>
</tbody>
</table>

#### Preferred

- **Lopinavir/ritonavir**
  - Coformulated liquid and tablet formulations
  - Tablets can be given without regard to food but may be better tolerated when taken with food or snack
  - Poor palatability of liquid (bitter taste), although better than ritonavir alone
  - Food effect (liquid should be administered with food)
  - Ritonavir component associated with large number of drug interactions (see ritonavir)
  - Use with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of electrocardiogram)

#### Alternative

- **Atazanavir in combination with low-dose ritonavir in children age ≥6 years**
  - Once-daily dosing
  - Atazanavir has less effect on triglyceride and total cholesterol levels than other PIs (but ritonavir boosting may be associated with elevations in these parameters)
  - No liquid formulation
  - Food effect (should be administered with food)
  - Indirect hyperbilirubinemia common but asymptomatic
  - Use with caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)

- **Fosamprenavir in combination with low-dose ritonavir in children age ≥6 years**
  - Oral prodrug of amprenavir with lower pill burden
  - Pediatric formulation available
  - Can give with food
  - Skin rash
  - More limited pediatric experience than preferred PI
  - Food effect (should be given with food)
  - Ritonavir component associated with large number of drug interactions (see ritonavir)
  - Contains sulfal moiety; potential for cross sensitivity between fosamprenavir and other drugs in sulfonamide class is unknown.

- **Darunavir in combination with low-dose ritonavir in children age ≥6 years**
  - Effective in PI-experienced children when given with low-dose ritonavir boosting
  - Pediatric data limited to antiretroviral-experienced children
  - Pediatric pill burden high with current tablet dose formulations
  - No liquid formulation
  - Food effect (should be given with food)
  - Must be given with ritonavir boosting to achieve adequate plasma concentrations
  - Contains sulfal moiety; potential for cross sensitivity between darunavir and other drugs in sulfonamide class is unknown.
### Advantages and Disadvantages of Different Protease Inhibitors (PIs) for Use in Highly Active Antiretroviral Combination Regimens for Initial Therapy in Children

#### Use in Special Circumstances

<table>
<thead>
<tr>
<th>PI Type</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Fosamprenavir (unboosted) in children age ≥2 years | • Oral prodrug of amprenavir with lower pill burden  
• Pediatric formulation available  
• Can give with food | • Skin rash  
• More limited pediatric experience than preferred PI  
• May require boosted regimen to achieve adequate plasma concentrations but pharmacokinetic data to define appropriate dosing not yet available |
| Atazanavir (unboosted) in treatment-naïve adolescents age ≥13 years and >39 kg who are unable to tolerate ritonavir | • Once-daily dosing  
• Less effect on triglyceride and total cholesterol levels than other PIs | • No liquid formulation  
• Food effect (should be administered with food)  
• Indirect hyperbilirubinemia common but asymptomatic  
• Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)  
• May require ritonavir boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations  
| Nelfinavir in children age ≥2 years | • Powder formation (for liquid preparation or to be added to food)  
• Can give with food  
• Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate | • Diarrhea  
• Powder formulation poorly tolerated  
• Food effect (should be administered with food)  
• Appropriate dosage for younger children not well defined  
• Need for 3 times daily dosing for younger children  
• Adolescents may require higher doses than adults  
| Not Recommended | | |
| Atazanavir (unboosted) in children <13 years of age and/or <39 kg | • Once-daily dosing (>13 years)  
• Less effect on triglyceride and total cholesterol levels than other PIs | • Drug levels low if used without ritonavir boosting  
• No liquid formulation  
• Food effect (should be administered with food)  
• Indirect hyperbilirubinemia common but asymptomatic  
• Use in caution in patients with pre-existing conduction system defects (can prolong PR interval of electrocardiogram)  
• May require ritonavir boosting in treatment-naïve adolescent patients to achieve adequate plasma concentrations |
| Indinavir (unboosted or boosted) | • May be considered for use as component of a regimen in combination with low-dose ritonavir in postpubertal adolescents who weigh enough to receive adult dosing | • Only available in capsule  
• Possible higher incidence of nephrotoxicity in children  
• Requires 3 times daily dosing unless boosted with ritonavir  
• High fluid intake required to prevent nephrolithiasis  
• Food effect (should be taken 1 hour before or 2 hours after food)  
• Limited pediatric pharmacokinetic data |
| Tipranavir | • Effective in PI-experienced children and adults when given with low-dose ritonavir boosting  
• Liquid formulation | • Limited data in treatment-naïve patients  
• Food effect (should be administered with food)  
• Must be given with ritonavir boosting to achieve adequate plasma concentrations |
| Ritonavir (full dose) | • Liquid formulation  
• Can be given with food | • Poor palatability of liquid (bitter taste)  
• Gastrointestinal intolerance  
• Food effect (should be administered with food)  
• Largest number drug interactions (most potent inhibitor of CYP3A4) |
<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| **Nelfinavir in children age <2 years** | • Powder formation (for liquid preparation or to be added to food)  
• Can give with food  
• Simplified 2 tablets (625 mg) twice-daily regimen has a reduced pill burden compared with other PI-containing regimens in older patients where the adult dose is appropriate | • Diarrhea  
• Powder formulation poorly tolerated  
• Food effect (should be administered with food)  
• Appropriate dosage for younger children not well defined  
• Need for 3 times daily dosing for younger children  
• Adolescents may require higher doses than adults  
• Less potent that boosted PIs |
| **Saquinavir (unboosted or boosted)**    | • Low bioavailability, should never be used as sole PI  
• Limited pediatric pharmacokinetic data; will require boosting with another PI (e.g., ritonavir) to achieve adequate concentrations  
• No liquid formulation  
• High pill burden  
• Must be taken with food  
• Photosensitivity reactions can occur |
### Table 13. Advantages and Disadvantages of Entry Inhibitors for Use in Highly Active Antiretroviral Combination Regimens

<table>
<thead>
<tr>
<th>General Issues</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry Inhibitors</td>
<td><strong>Entry Inhibitor Class Advantages:</strong></td>
<td><strong>Entry Inhibitor Class Disadvantages:</strong></td>
</tr>
<tr>
<td><strong>Susceptibility of HIV to a new class of ARVs</strong></td>
<td>• Rapid development of resistance with enfuvirtide</td>
<td></td>
</tr>
<tr>
<td><strong>Route of administration ensures adequate drug levels</strong></td>
<td>• CCR5 inhibitors ineffective against CXCR4 virus, mixed CCR5 and CXCR4 viral populations, or dual-tropic virus</td>
<td></td>
</tr>
<tr>
<td>Use in Special Circumstances</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Enfuvirtide</strong></td>
<td>• Susceptibility of HIV to a new class of ARVs</td>
<td><strong>Twice-daily subcutaneous injections</strong></td>
</tr>
<tr>
<td></td>
<td>• Route of administration ensures adequate drug levels</td>
<td><strong>98%–100% incidence of local injection site reactions</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Poor adherence and limited levels of success in adolescents due to local site reactions</strong></td>
</tr>
<tr>
<td>Insufficient Data to Recommend</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maraviroc</strong></td>
<td>• Susceptibility of HIV to a new class of ARVs</td>
<td><strong>Ineffective against CXCR4 or mixed/dual-tropic viral populations</strong></td>
</tr>
<tr>
<td></td>
<td>• Can give with food</td>
<td><strong>Limited data on pediatric dosing or safety</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>No pediatric formulation</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Multiple drug interactions; different dosing depending on which NNRTI or PI is coadministered</strong></td>
</tr>
</tbody>
</table>

### Table 14. Advantages and Disadvantages of Integrase Inhibitors for Use in Highly Active Antiretroviral Combination Regimens

<table>
<thead>
<tr>
<th>General Issues</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrase Inhibitors</td>
<td><strong>Integrase Inhibitor Class Advantages:</strong></td>
<td><strong>Integrase Inhibitor Class Disadvantages:</strong></td>
</tr>
<tr>
<td><strong>Susceptibility of HIV to a new class of ARVs</strong></td>
<td>• Limited data on pediatric dosing or safety</td>
<td></td>
</tr>
<tr>
<td>Insufficient Data to Recommend</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raltegravir</strong></td>
<td>• Susceptibility of HIV to a new class of ARVs</td>
<td><strong>Limited data on pediatric dosing or safety</strong></td>
</tr>
<tr>
<td></td>
<td>• Can give with food</td>
<td><strong>No pediatric formulation</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Rare systemic allergic reaction or hepatitis</strong></td>
</tr>
</tbody>
</table>
antiretroviral medications, please see Tables 17a–17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations.

Table 15. Example of Minimum Schedule for Monitoring of Children on Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Time Schedule for Monitoring</th>
<th>Toxicity Monitoring¹</th>
<th>Efficacy and Adherence Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (prior to initiation of therapy)</td>
<td>Clinical history, complete blood count and differential, chemistries³</td>
<td>CD4 cell count/percentage, HIV RNA</td>
</tr>
<tr>
<td>1–2 weeks²</td>
<td>Clinical history</td>
<td>Adherence screen</td>
</tr>
<tr>
<td>4–8 weeks</td>
<td>Clinical history, complete blood count and differential, chemistries³</td>
<td>CD4 cell count/percentage⁴, HIV RNA, adherence screen</td>
</tr>
<tr>
<td>Every 3–4 months</td>
<td>Clinical history, complete blood count and differential, chemistries³</td>
<td>CD4 cell count/percentage, HIV RNA, adherence screen</td>
</tr>
<tr>
<td>Every 6–12 months</td>
<td>Lipid panel</td>
<td></td>
</tr>
</tbody>
</table>

¹ For children receiving nevirapine, serum transaminase levels should be measured every 2 weeks for the first 4 weeks of therapy, then monthly for 3 months, followed by every 3 to 4 months.

² Children starting a new antiretroviral regimen should be evaluated in person or by phone within 1 to 2 weeks of starting medication to screen for clinical side effects and to ensure patient adherence to the regimen. Many clinicians will plan additional contacts (in person or by telephone) with the child and caregivers to support adherence during the first few weeks of therapy. Some clinicians also recommend an HIV RNA measurement within the initial weeks of therapy for an early assessment of response/adherence to therapy.

³ Chemistries may include electrolytes, glucose, liver function tests (hepatic transaminases and bilirubin), renal function tests (BUN, creatinine), calcium, and phosphate. Additional evaluations should be tailored to the particular drugs the child is receiving; for example, pancreatic enzymes (amylase and lipase) may be considered if the child is starting drugs with potential pancreatic toxicity, such as didanosine.

⁴ Some clinicians do not recommend a CD4 cell count/percentage at this time, considering it too early to expect an immunologic response.
Table 16. Strategies to Improve Adherence with Antiretroviral Medications

<table>
<thead>
<tr>
<th>Initial Intervention Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Establish trust and identify mutually acceptable goals for care.</td>
</tr>
<tr>
<td>• Obtain explicit agreement on need for treatment and adherence.</td>
</tr>
<tr>
<td>• Identify depression, low self-esteem, drug use, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat prior to starting antiretroviral drugs, if possible.</td>
</tr>
<tr>
<td>• Identify family, friends, health team members, or others who can help with adherence support.</td>
</tr>
<tr>
<td>• Educate patient and family about the critical role of adherence in therapy outcome.</td>
</tr>
<tr>
<td>• Specify the adherence target: ≥95% of prescribed doses.</td>
</tr>
<tr>
<td>• Educate patient and family about the relationship between partial adherence and resistance.</td>
</tr>
<tr>
<td>• Educate patient and family about resistance and constraint of later choices of antiretroviral drug (i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent).</td>
</tr>
<tr>
<td>• Develop a treatment plan that the patient and family understand and to which they feel committed.</td>
</tr>
<tr>
<td>• Establish readiness to take medication by practice sessions or other means.</td>
</tr>
<tr>
<td>• Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Choose the simplest regimen possible, reducing dosing frequency and number of pills.</td>
</tr>
<tr>
<td>• Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities.</td>
</tr>
<tr>
<td>• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).</td>
</tr>
<tr>
<td>• Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects.</td>
</tr>
<tr>
<td>• Simplify food requirements for medication administration.</td>
</tr>
<tr>
<td>• Prescribe drugs carefully to avoid adverse drug-drug interactions.</td>
</tr>
<tr>
<td>• Assess pill swallowing capacity and offer pill swallowing training.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Intervention Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Monitor adherence at each visit and in between visits by telephone or letter as needed.</td>
</tr>
<tr>
<td>• Provide ongoing support, encouragement, and understanding of the difficulties of the demands of attaining ≥95% adherence with medication doses.</td>
</tr>
<tr>
<td>• Use patient education aids including pictures, calendars, and stickers.</td>
</tr>
<tr>
<td>• Use pill boxes, reminders, alarms, pagers, and timers.</td>
</tr>
<tr>
<td>• Provide follow-up clinic visits or telephone calls to support and assess adherence.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• Provide pharmacist-based adherence support.</td>
</tr>
<tr>
<td>• Consider gastrostomy tube use in selected circumstances.</td>
</tr>
<tr>
<td>• Consider a brief period of hospitalization for selected circumstances of apparent virologic failure to assess adherence and reinforce that medication adherence is fundamental to successful antiretroviral therapy.</td>
</tr>
<tr>
<td>• Consider directly observed therapy at home, in the clinic, or during a brief inpatient hospitalization.</td>
</tr>
</tbody>
</table>
### Table 17a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hematologic Effects

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic Effects: Anemia*</td>
<td>Principally ZDV</td>
<td>Onset: Variable, weeks to months</td>
<td>HIV-exposed newborns:</td>
<td>HIV-exposed newborns:</td>
<td>HIV-exposed newborns:</td>
<td>HIV-exposed newborns:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td>• Uncommon but coincident with physiologic Hgb nadir</td>
<td>• Premature birth In utero exposure to ARVs</td>
<td>• Monitor CBC at birth.</td>
<td>• Rarely require intervention unless Hgb is &lt;7.0 gm/dL or anemia is associated with symptoms.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most commonly asymptomatic or mild fatigue, pallor, tachypnea</td>
<td>HIV-infected children on ARVs:</td>
<td>Advanced maternal HIV disease</td>
<td>Consider repeat CBC at 4 weeks for higher risk babies (exposed to ARVs in utero or as neonates, premature birth, or low birth Hgb).</td>
<td>• Consider discontinuing ZDV if ≥4 weeks of 6-week ZDV prophylaxis regimen are already completed. (see Perinatal Guidelines).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rarely, congestive heart failure</td>
<td>HIV-infected children on ARVs:</td>
<td>Neonatal blood loss</td>
<td>HIV-infected children on ARVs:</td>
<td>HIV-infected children on ARVs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2–3 times more common with ZDV-containing regimens</td>
<td></td>
<td>• Avoid ZDV in children with anemia when alternative agents are available.</td>
<td>• Discontinue non-ARV marrow-toxic drugs if feasible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Less frequent in recent studies, possibly due to lower dosing of ZDV</td>
<td></td>
<td>• Monitor CBC 3–4 times per year as part of routine care.</td>
<td>• Treat coexisting iron deficiency, OIs, malignancies.</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td>• Rarely necessary to discontinue ARV therapy.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• For persistent anemia thought to be associated with ARVs:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>o change to a non-ZDV-containing regimen;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o give erythropoietin 50–200 IU/kg/dose 3 times weekly.</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td><strong>Associated ARVs</strong></td>
<td><strong>Onset/Clinical Manifestations</strong></td>
<td><strong>Estimated Frequency</strong></td>
<td><strong>Risk Factors</strong></td>
<td><strong>Prevention/Monitoring</strong></td>
<td><strong>Management</strong></td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------</td>
<td>----------------------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>Principally ZDV</td>
<td>Onset: Variable</td>
<td>HIV-exposed newborns:</td>
<td>HIV-exposed newborns:</td>
<td>HIV-infected children on ARVs:</td>
<td>HIV-infected children on ARVs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td>• Rare</td>
<td>• <em>In utero</em> exposure to ARVs</td>
<td>• Poorly controlled HIV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HIV-infected children on ARVs:</td>
<td></td>
<td>• Marrow-toxic drugs (e.g., trimethoprim-sulfamethoxazole, ganciclovir, hydroxyurea, rifabutin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 9.9%–26.8% of children on ARVs, depending upon the ARV regimen</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Higher with ZDV-containing regimens</td>
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</tr>
</tbody>
</table>

* HIV infection itself, opportunistic infections, and medications used to prevent OIs, such as trimethoprim-sulfamethoxazole, may all contribute to anemia, neutropenia, and thrombocytopenia.

† Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

**Key to Abbreviations:** ANC = absolute neutrophil count; ARVs = antiretrovirals; CBC = complete blood count; G6PD = glucose-6-phosphate dehydrogenase; G-CSF = granulocyte colony-stimulating factor; Hgb = hemoglobin; IU = International Unit; OIs = opportunistic infections; ZDV = zidovudine
Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic Events:</td>
<td>All ARVs</td>
<td>Onset:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic toxicity (elevated AST, ALT, clinical hepatitis)</td>
<td></td>
<td>• NNRTI and PI therapy: Within 12 weeks of initiation.</td>
<td></td>
<td>• HBV or HCV coinfection</td>
<td>Avoid concomitant use of hepatotoxic medications.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NRTI therapy: Within months to years of initiation.</td>
<td></td>
<td>• Elevated baseline ALT, AST</td>
<td>Monitoring: For ARVs other than NVP: Obtain AST, ALT at baseline and at least every 3–4 months or more frequently in at-risk patients (e.g., HBV or HCV coinfected, elevated baseline AST, ALT). For NVP: Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Any antiretroviral combination regimen: Early due to immune reconstitution inflammatory syndrome.</td>
<td></td>
<td>• Other hepatotoxic medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td>• Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Asymptomatic elevation of AST, ALT.</td>
<td></td>
<td>• Underlying liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May be associated with symptoms of clinical hepatitis including nausea, fatigue, and jaundice.</td>
<td></td>
<td>• For NVP-associated hepatic events in adults:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NRTIs, especially ZDV, ddl, d4T, may be associated with lactic acidosis and hepatic steatosis.</td>
<td></td>
<td>o female with pre-NVP CD4 &gt;250 cells/mm³</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Rarely, prolonged exposure to ddl is associated with non-cirrhotic portal hypertension with esophageal varices.</td>
<td></td>
<td>o male with pre-NVP CD4 &gt;400 cells/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Higher drug concentrations for PIs, particularly TPV</td>
<td></td>
<td>• Higher drug concentrations for PIs, particularly TPV</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• Uncommon in children.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• Frequency varies with different agents and drug combinations (NVP, TPV of particular concern).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Avoid concomitant use of hepatotoxic medications.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitoring: For ARVs other than NVP: Obtain AST, ALT at baseline and at least every 3–4 months or more frequently in at-risk patients (e.g., HBV or HCV coinfected, elevated baseline AST, ALT). For NVP: Obtain AST, ALT at baseline, at 2 and 4 weeks, then every 3 months.</td>
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<tr>
<td></td>
<td></td>
<td>In asymptomatic patients with ALT or AST &gt;5–10 times ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• If hepatic enzymes elevated &gt;5–10 times ULN, most clinicians would avoid NVP.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• In asymptomatic patients, discontinue all ARVs and other potential hepatotoxic agents and avoid restart of the offending agent.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• If a symptomatic hepatic event occurs on NVP, permanently discontinue NVP (see also NVP hypersensitivity).</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• When clinical hepatitis is associated with lactic acidosis, avoid restart of the most likely agent, NRTIs, ZDV, d4T,</td>
<td></td>
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</tr>
</tbody>
</table>
Table 17b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Hepatic Events

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect hyperbilirubinemia</td>
<td>IDV, ATV</td>
<td>Onset: Early in therapy. Presentation: • Jaundice. • Asymptomatic elevation of indirect bilirubin levels.</td>
<td>HIV-infected children receiving ATV: 49% developed increased total bilirubin levels (≥3.2 mg/dL); 13% had jaundice/scleral icterus.</td>
<td>Not associated with HBV or HCV.</td>
<td>Monitoring: Assess bilirubin levels periodically, especially in first few months on regimen.</td>
<td>Not necessary to discontinue the offending agent except for cosmetic reasons (hyperbilirubinemia may improve over time).</td>
</tr>
</tbody>
</table>

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ALT = alanine transaminase; ARVs = antiretrovirals; AST = aspartate aminotransferase; ATV = atazanavir; CMV = cytomegalovirus; d4T = stavudine; ddI = didanosine; EBV = Epstein-Barr virus; FTC = emtricitabine; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

**References**

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Insulin resistance, asymptomatic hyperglycemia, diabetes mellitus (DM)* | • Thymidine analogue NRTIs (d4T > ZDV) • Some PIs but unclear if class effect | Onset: Weeks to months after beginning therapy; median = 60 days (adult data)  
Presentation:  
- Most commonly: Asymptomatic fasting hyperglycemia, possibly in the setting of lipodystrophy, metabolic syndrome, or growth delay  
- Also possible: Frank DM (polyuria, polydipsia, polyphagia, fatigue, hyperglycemia) | Impaired fasting glucose:  
- ARV-treated adults: 3%–25%  
- ARV-treated children: 0%–7%  
Impaired glucose tolerance:  
- ARV-treated adults: 16%–35%  
- ARV-treated children: 3%–4%  
DM:  
- ARV-treated adults: 1.2–4.7 per 100 person-years (2–4-fold greater than that for non-HIV-infected adults)  
- ARV-treated children: Very rare in HIV-infected children | Risk factors for Type 2 DM:  
- Lipodystrophy, metabolic syndrome  
- Family history of DM  
- Overweight, obesity | Prevention:  
- Lifestyle modification (see Management).  
- Although uncertain, avoiding use of d4T, PI-containing regimens might reduce risk.  
Monitoring:  
- Monitor for polydipsia, polyuria, polyphagia, change in body habitus, acanthosis nigricans.  
- Obtain random plasma glucose (RPG) levels at:  
  o initiation of ARV therapy;  
  o 3–6 months later; and  
  o annually thereafter.  
- For RPG ≥140 mg/dL, obtain fasting plasma glucose (FPG) performed after 8-hour fast and consider referral to endocrinologist.  
- FPG 100–125 mg/dL: Impaired FPG is suggestive of insulin resistance; consult endocrinologist.  
- FPG <100 mg/dL: Suggests no current insulin resistance; recheck in 6–12 months. | Counsel lifestyle modification (low fat diet, exercise, no smoking).  
Consider changing from thymidine analogue NRTI (d4T or ZDV)-containing regimen.  
For either RPG ≥200 mg/dL plus symptoms of DM or FPG ≥126 mg/dL: Diagnostic criteria for DM are met; consult endocrinologist.  
- FPG 100–125 mg/dL: Impaired FPG is suggestive of insulin resistance; consult endocrinologist.  
- FPG <100 mg/dL: Suggests no current insulin resistance; recheck in 6–12 months. |
Insulin resistance, asymptomatic hyperglycemia, and diabetes mellitus form a spectrum of increasing severity. Insulin resistance is often defined as elevated insulin levels for the level of glucose observed; impaired fasting plasma glucose (impaired FPG) as an FPG of 100–125 mg/dL; impaired glucose tolerance is an elevated 2-hour PG of 140–199 mg/dL in a standard oral glucose tolerance test (OGTT); and diabetes mellitus as either a FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, a HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥200 mg/dL. However, the Panel does not recommend routine determinations of insulin levels, glycosylated hemoglobin A1C, or glucose tolerance without consultation with an endocrinologist; these guidelines are instead based on the readily available random and fasting plasma glucose levels.

Key to Abbreviations: ARV = antiretroviral; d4T = stavudine; DM = diabetes mellitus; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

References

Clinical features of hyperglycemia, insulin resistance, and diabetes mellitus

## Table 17d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Dyslipidemia

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Dyslipidemia    | PIs: All PIs; lower incidence with ATV  
NRTIs: Especially d4T | Onset: Weeks to months after beginning therapy  
Presentation: PIs: ↑LDL-C, TC, and TG  
NNRTIs: ↑LDL-C, TC, and HDL-C  
NRTIs: ↑LDL-C, TC, and TG | 20%–50% of children receiving combination antiretroviral therapy will have lipoprotein abnormalities. | • HIV infection  
• Poor diet  
• Lack of exercise  
• Obesity  
• Hypertension  
• Smoking  
• Family history of dyslipidemia or premature CVD  
• Metabolic syndrome | Prevention: Low fat diet, exercise, no smoking.  
Monitoring: Adolescents and adults: Obtain fasting (12-hour) TC, HDL-C, TG, LDL-C prior to initiating or changing ARV therapy, 3–6 months thereafter, then every 6–12 months.  
Children without lipid abnormalities or risk factors: Obtain nonfasting screening lipid profiles prior to initiating or changing therapy and every 6–12 months if stable. If TG or LDL-C is elevated, obtain fasting blood tests.  
Children with lipid abnormalities and/or additional risk factors: Obtain fasting (12-hour) TC, HDL-C, TG, LDL-C prior to initiating or changing therapy and every 6 months (or more often if indicated).  
Children receiving lipid-lowering therapy with statins or fibrates: Obtain fasting (12-hour) lipid profiles, liver function tests (LFTs), and creatine kinase (CK) prior to initiating lipid therapy and at 4 weeks and 8 weeks after starting lipid therapy. If minimal | • Counsel lifestyle modification (low fat diet, exercise, smoking cessation) for adequate trial period (3–6 months).  
• Switch to a new ARV regimen less likely to cause lipid abnormalities.  
Pharmacologic Management:  
• Prompt intervention is required in patients with TG ≥500 mg/dL (high risk of pancreatitis).  
• Statins such as pravastatin or atorvastatin†  
• Fibrates such as gemfibrozil and fenofibrate may be used as alternative agents for adults with ↑TG but are not approved for use in children.  
• N-3 polyunsaturated fatty acids (PUFAs) derived from fish oils  
• No consensus as to what LDL-C should prompt treatment in children receiving ARVs ‡  
○ High-risk patients: |
* The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

† Statins are teratogenic and should not be used in female patients who may become pregnant. Serious toxicities include hepatotoxicity, skeletal muscle toxicity, and rhabdomyolysis. Experience with statins limited to children >6 years of age. Multiple drug interactions with lipid-lowering agents and ARVs.

Pravastatin (Pravachol)
8–13 years of age: 20 mg once daily; 14–18 years of age: 40 mg once daily

Atorvastatin (Lipitor)
>6 years of age: 10–20 mg once daily

‡ It is unclear what the long-term risks of lipid abnormalities are in children receiving combination antiretroviral therapy. However, persistent dyslipidemia in children is likely to lead to premature cardiovascular disease.

**Key to Abbreviations:** ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; CVD = cardiovascular disease; d4T = stavudine; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TC = total cholesterol; TG = triglycerides; ZDV = zidovudine

**References**


### Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>NVP, EFV, ETR, FPV, ATV, FTC ABC, DRV, TPV, TDF, LPV/r, RAL, MVC</td>
<td>Onset: The first few days to weeks after starting therapy. Presentation: Most rashes are mild-to-moderate, diffuse maculopapular eruptions. Some rashes are a manifestation of systemic hypersensitivity (see also hypersensitivity reaction).</td>
<td>Common (&gt;10% adults and/or children): NVP, EFV, ETR, FPV, ATV, FTC Less common (5%–10%): ABC, DRV, TPV, TDF Unusual (2%–4%): LPV/r, RAL, MVC</td>
<td>• Rash with a sulfonamide is a risk factor for rash with NNRTIs and the PIs containing a sulfonamide moiety (FPV, APV, DRV, TPV). • Possible association of the HLA-DRB 101 allele with rash with NVP or EFV. When starting NVP or restarting after interruptions ≥7 days: • Once-daily dosing for 2 weeks (50% of total daily dose), then escalation to target dose with twice-daily dosing is associated with fewer rashes.</td>
<td>When starting NVP or restarting after interruptions ≥7 days:</td>
<td>Mild-to-moderate rash: • Prescribe antihistamine as needed; the antiretroviral medication can be continued.*</td>
</tr>
</tbody>
</table>
### Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

<table>
<thead>
<tr>
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<th>Associated ARVs</th>
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<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENF</td>
<td></td>
<td>Onset: The first few days to weeks after starting therapy.</td>
<td>Adults: &gt;90% (resulted in ENF discontinuation in 7%)</td>
<td>Unknown</td>
<td>• During routine visits assess patient for local reactions.</td>
<td>elevated, NVP should be discontinued and not restarted (see NVP hypersensitivity).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation: Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritis, ecchymosis. Often multiple reactions at the same time.</td>
<td></td>
<td></td>
<td>• Rotate injection sites.</td>
<td>• Continue the agent as tolerated by the patient, adjust injection technique, and rotate injection sites.</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome (SJS)/erythema multiforme major (EM)/toxic epidermal necrolysis (TEN)</td>
<td>NVP, EFV, ETR, FPV, ABC, DRV, ZDV, ddl, IDV, LPV/r, ATV</td>
<td>Onset: The first few days to weeks after initiating therapy.</td>
<td>Infrequent: NVP (0.3%), EFV (0.1%), ETR (&lt;0.1%)</td>
<td>Adults:</td>
<td>• For NVP, 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may prevent the rash.*</td>
<td>For NVP, 2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may prevent the rash.*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation: Skin eruption occurs with mucous membrane ulceration, conjunctivitis. Can evolve into blister/bullae formation and can progress to skin necrosis. Systemic symptoms may include fever, tachycardia, malaise, myalgia, arthralgia.</td>
<td></td>
<td></td>
<td>• Case reports: FPV, ABC, DRV, ZDV, ddl, IDV, LPV/r, ATV</td>
<td>• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. May need intensive care support, intravenous hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics in case of superinfection. Corticosteroids and/or IVIG are sometimes used but use of each is controversial. Do not reintroduce the offending</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• During routine visits assess patient for local reactions.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rotate injection sites.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Massage area after injection.</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Continue the agent as tolerated by the patient, adjust injection technique, and rotate injection sites.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Discontinue all ARVs and other possible causative agents such as cotrimoxazole. May need intensive care support, intravenous hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics in case of superinfection. Corticosteroids and/or IVIG are sometimes used but use of each is controversial. Do not reintroduce the offending</td>
<td></td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Associated ARVs</td>
<td>Onset/Clinical Manifestations</td>
<td>Estimated Frequency</td>
<td>Risk Factors</td>
<td>Prevention/ Monitoring</td>
<td>Management</td>
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</tr>
<tr>
<td>Systemic hypersensitivity reaction (HSR)</td>
<td>ABC</td>
<td>Onset: Within the first 6 weeks with first use; within hours with reintroduction. Presentation: Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms such as dyspnea. Symptoms worsen to include hypertension and vascular collapse with continuation. Symptoms can mimic anaphylaxis with rechallenge.</td>
<td>2.3%–9% (varies by racial/ethnic group)</td>
<td>HLA-B<em>5701 (HSR very uncommon in people who are HLA-B</em>5701 negative); also HLA-DR7, HLA-DQ3. Whites are at much greater risk of HSR than blacks or Asians.</td>
<td>Screen for HLA-B<em>5701. ABC should not be prescribed if HLA-B</em>5701 is positive. The patient should be labeled as ABC allergic in the medical record. Counsel families about the signs and symptoms of HSR to ensure prompt reporting of reactions.</td>
<td>Discontinue ARVs and investigate for other causes of the symptoms such as an intercurrent viral illness. Treat symptoms as necessary. Most symptoms resolve by 48 hours after discontinuation of ABC. Do not rechallenge with ABC even if the patient is HLA-B*5701 negative.</td>
</tr>
<tr>
<td>NVP</td>
<td>Onset: Most frequent in the first few weeks of therapy but can occur through 18 weeks. Presentation: Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without rash.</td>
<td>4% (2.5%–11%) For adults: Treatment naïve with higher CD4 count (&gt;250 cells/mm³ in women; &gt;400 cells/mm³ in men) Females 3-fold higher risk than males NVP</td>
<td>2-week lead-in period for start or restart for interruptions ≥7 days with once-daily dosing then dose escalation to twice daily as recommended may reduce rash and hepatic events.</td>
<td>Discontinue ARVs. Consider other causes for hepatitis and discontinue all hepatotoxic medications. Provide supportive care as indicated and close monitoring. Do not reintroduce NVP. The safety of other NNRTIs is...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 17e. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR
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<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
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<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ENF</td>
<td>Onset: Any time during therapy. Presentation: Symptoms may include rash, fever, nausea, vomiting, rigors, hypertension, elevated hepatic transaminases.</td>
<td>&lt;1%</td>
<td>Unknown.</td>
<td>• Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td>Discontinue ARVs. Rechallenge with ENF is not recommended.</td>
</tr>
</tbody>
</table>

- without skin rash that may progress to hepatic failure with encephalopathy. DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has also been described.
- hepatoxicitiy and hypersensitivity may be less common in prepubertal children than in adults.

- Enfuvirtide (EnF)

- Counseling families about signs and symptoms of HSR to ensure prompt reporting of reactions.
- Obtain AST and ALT in patients with rash.
- Obtain AST and ALT at baseline, prior to dose escalation, 2 weeks post dose escalation, and at 3-month intervals thereafter.
- Avoid use in women with CD4 >250 cells/mm³ and in men with CD4 >400 cells/mm³ unless benefits outweigh risks.
- Do not use NVP in postexposure prophylaxis.

- unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.
Table 17e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Skin Rash, SJS/EM/TEN, HSR

* The prescribing information for nevirapine states that patients experiencing rash during the 14-day lead-in period should not have the nevirapine dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase the risk of nevirapine resistance due to subtherapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and consultation with an expert in HIV care should be obtained. Nevirapine should be stopped if the rash is severe or is worsening or progressing.

Key to Abbreviations: ABC = abacavir; ALT = alanine transaminase; APV = amprenavir; ARVs = antiretrovirals; AST = aspartate aminotransferase; ATV = atazanavir; ddl = didanosine; DRV = darunavir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; ETR = etravirine; FTC = emtricitabine; FPV = fosamprenavir; HSR = hypersensitivity reaction; IDV = indinavir; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; SJS = Stevens Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

References

### Table 17f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lipodystrophy, Lipohypertrophy, Lipoatrophy

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Lipodystrophy—General information | | Onset: Trunk and limb fat initially increases within a few months of start of ART; however, peripheral fat wasting may not begin to appear for 12–24 months. | Adults: 2%–84%  
Children: 1%–33%, perhaps more common in adolescents than prepubertal children | • Genetic predisposition  
• Puberty  
• HIV-associated inflammation | See above | |
| Central lipohypertrophy | • Most associated with PIs and EFV  
• Can occur in the absence of ART | Presentation: Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia. The appearance of central lipohypertrophy is accentuated in the presence of peripheral fat wasting (lipoatrophy). In adults, waist circumference >102 cm (men) or >88 cm (women) is associated with increased risk of metabolic syndrome. For children and adolescents, waist circumference above the 75% percentile for age is associated with increased risk of metabolic syndrome. | See above | • PIs  
• EFV | Prevention: Diet and exercise.  
Monitoring: Measure waist circumference, waist to height ratio, and/or BMI (increase of each associated with development of metabolic syndrome). | • Diet and exercise, especially strength training.  
• Liposuction (Lipohypertrophy may reoccur after this cosmetic procedure; liposuction is not recommended for children.)  
• Recombinant human growth hormone or growth hormone-releasing hormone (investigational).  
• Metformin and rosiglitazone are not useful for treatment. |
### Key to Abbreviations:
- ART = antiretroviral therapy
- ARVs = antiretrovirals
- BMI = body mass index
- d4T = stavudine
- DXA = dual energy x-ray absorptiometry
- EFV = efavirenz
- FDA = Food and Drug Administration
- NRTI = nucleoside reverse transcriptase inhibitor
- PI = protease inhibitor
- ZDV = zidovudine

### References
(See the archived version of Supplement III, February 23, 2009 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, [http://www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov) for a more complete discussion and reference list.)

### General Reviews

### Associated ARVs/Etiology
### Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>NRTIs, in particular, d4T and ddI (each and in combination)</td>
<td>Onset: 1–20 months after starting therapy (median onset 4 months in one case series). Presentation: • Usually insidious onset of a combination of signs and symptoms: o Generalized fatigue, weakness, and myalgias o Vague abdominal pain, sudden weight loss, unexplained nausea or vomiting o Dyspnea o Peripheral neuropathy. • Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, and respiratory failure).</td>
<td>Chronic, asymptomatic mild hyperlactatemia (2.1–5.0 mmol/L):  o Adults: 15%–35% of those receiving NRTI therapy longer than 6 months  o Children: 29%–32%</td>
<td>Adult risk factors:  • Female gender  • High BMI  • Chronic HCV infection  • African-American race  • Prolonged NRTI use (particularly d4T and ddI)  • Coadministration of ddI with other agents (e.g., d4T, TDF, ribavirin, or tetracycline)  • CD4 count &lt;350 cells/mm³  • Acquired riboflavin or thiamine deficiency  • Possibly pregnancy</td>
<td>Prevention:  • Avoidance of d4T and ddI in combination.  • Early recognition of clinical manifestations and adjustment of therapy. Monitoring:  • Asymptomatic: Measurement of serum lactate is not recommended.  • Clinical signs or symptoms consistent with lactic acidosis: Obtain blood lactate level¹; additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.</td>
<td>Lactate 2.1–5.0 mmol/L (confirmed with second test):  • Consider replacing ddI and d4T with other ARVs.  • As alternative, temporarily discontinue all ARVs while conducting additional diagnostic work-up. Lactate &gt;5.0 mmol/L (confirmed with second test)¹ or &gt;10.0 mmol/L (any one test):  • Discontinue all ARVs.  • Provide supportive therapy (intravenous fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues).  • Anecdotal (unproven) supportive therapies: bicarbonate infusions, tris–hydroxymethylaminomethane (THAM), high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q, vitamin C).  • Following resolution of...</td>
</tr>
</tbody>
</table>
### Table 17g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Lactic Acidosis

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
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</tbody>
</table>

- Blood for lactate determination should be collected without prolonged tourniquet application or fist clenching into a prechilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

† Management may be initiated before the results of the confirmatory test.

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ARVs = antiretrovirals; BMI = body mass index; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; NRTI = nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate

**References**

**General Reviews**

### Table 17h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations – Osteopenia, Osteoporosis, Osteonecrosis

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Osteopenia and osteoporosis          | Following initiation of combination therapy, regardless of regimen. | Onset: Any age; greatest risk in months after initiation of associated ARV | Low bone density: 20% of children treated with combination ARV therapy had BMD z score <-1.5 | • Longer duration of HIV infection  
• Greater severity of HIV disease  
• Growth delay, pubertal delay  
• Low BMI  
• Lipodystrophy  
• Nonblack race  
• Smoking  
• Steroid use, medroxyprogesterone | Prevention:  
• Ensure calcium and vitamin D sufficiency.  
• Encourage weight-bearing exercise.  
• Reduce modifiable risk factors (smoking, low BMI, steroids, medroxyprogesterone).  
• Role of bisphosphonates not established in children.  
• Consider change in ARV regimen. | • Ensure calcium and vitamin D sufficiency.  
• Encourage weight-bearing exercise.  
• Reduce modifiable risk factors (smoking, low BMI, steroids, medroxyprogesterone).  
• Role of bisphosphonates not established in children.  
• Consider change in ARV regimen. |
|                                      | Specific agents of possible concern: TDF, d4T, or PIs.                     | Presentation: Most commonly asymptomatic; fracture (rare) | Note: Osteoporosis diagnosis in children requires clinical evidence of bone fragility and cannot rely solely on measured low bone density. |                                                                                           |                                                                                                       |                                                                                                      |
| Osteonecrosis                        | No specific ARV identified. May be related to HIV infection itself.       | Onset: Any age                  | Prevalence: 0.2% in children  
Incidence: 0.03% per year in children | Children: Unknown  
Adults:  
• Steroid use  
• Alcohol abuse  
• Hemoglobinopathies  
• Hyperlipidemia  
• Pancreatitis  
• Osteopenia, osteoporosis  
• Hypercoagulable states | Prevention: Minimize steroid and alcohol use.  
Monitoring: Consider diagnostic evaluation in patients with unexplained limp, hip or other periarticular pain. | Confirm diagnosis: Plain radiographs and MRI; bone scan or CT if negative x-ray/MRI but clinical suspicion high.  
Treatment:  
• Early stages: decreased weight bearing on affected joint and use of analgesic.  
• Later stages: surgical intervention. |

*Some experts would periodically measure 25-OH-Vitamin D, especially in HIV-infected urban youth because of high prevalence of vitamin D insufficiency.*
† Until more data are available about the long-term effects of tenofovir on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for children in early puberty who are initiating treatment with tenofovir.

**Key to Abbreviations:** ARVs = antiretrovirals; BMI = body mass index; CT = computed tomography; d4T = stavudine; DXA = dual energy x-ray absorptiometry; MRI = magnetic resonance imaging; PIs = protease inhibitors; TDF = tenofovir disoproxil fumarate

**References**

**Osteopenia and Osteoporosis**


**Osteonecrosis**

Table 18. Considerations for Changing Antiretroviral Therapy for Human Immunodeficiency Virus (HIV)-Infected Children

<table>
<thead>
<tr>
<th>Virologic Considerations *</th>
<th>Immunologic Considerations *</th>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incomplete viral response to therapy:</strong> Incomplete virologic response to therapy is defined for all children as a $&lt;1.0 \log_{10}$ decrease in HIV RNA copy number from baseline after 8–12 weeks of therapy, HIV RNA $&gt;400$ copies/mL after 6 months of therapy, or repeated HIV RNA above the level of detection using the most sensitive assay after 12 months of therapy. †</td>
<td><strong>Incomplete immunologic response to therapy:</strong> Failure in a child $&lt;5$ years of age with severe immune suppression (CD4 percentage $&lt;15%$) to improve CD4 values by $\geq 5$ percentage points or failure in a child $\geq 5$ years of age with severe immune suppression (CD4 $&lt;200$ cells/mm$^3$) to improve CD4 values by $\geq 50$ cells/mm$^3$ above baseline within the first year of therapy.</td>
<td><strong>Progressive neurodevelopmental deterioration:</strong> Two or more of the following on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction.</td>
</tr>
<tr>
<td><strong>Viral rebound:</strong> For children who have previously achieved undetectable plasma viral load in response to therapy, viral rebound is defined as subsequent, repeated detection of plasma HIV RNA on ultrasensitive PCR assays. Infrequent episodes of low level viremia ($&lt;1,000$ copies/mL) are common and not generally reflective of virologic failure, whereas repeated or persistent viremia (especially if $&gt;1,000$ copies/mL) more likely represents viral rebound. ‡</td>
<td><strong>Immunologic decline:</strong> Sustained decline of 5 percentage points in CD4 percentage below pretherapy baseline at any age or decline to below pretherapy baseline in absolute CD4 cell count in children who are $\geq 5$ years of age. §</td>
<td><strong>Growth failure:</strong> Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation.</td>
</tr>
<tr>
<td>At least two measurements (taken 1 week apart) should be performed before considering a change in therapy. †</td>
<td>Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 count of 250 cells/mm$^3$ to 150 cells/mm$^3$) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 count of 150 cells/mm$^3$ to 100 cells/mm$^3$) are of particular concern.</td>
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</tbody>
</table>

† The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained $1.5–2.0 \log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels. Additionally, virologic suppression may take longer in young children given their higher viral load at the time of initiation of therapy than in older children or adults.

‡ Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., $<5,000$ copies/mL), especially in children with limited treatment options. The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations and/or nonadherence.

§ Declines that represent a change to a more advanced category of immunosuppression compared with baseline (e.g., from CD4 percentage of 28% to 23% or from CD4 count of 250 cells/mm$^3$ to 150 cells/mm$^3$) or to more severe immunosuppression in those already suppressed at baseline (e.g., from CD4 percentage of 14% to 9% or from CD4 count of 150 cells/mm$^3$ to 100 cells/mm$^3$) are of particular concern.
### Table 19. Assessment of Antiretroviral Treatment Failure

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Method</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence</strong></td>
<td>1. Interview child and caretaker</td>
<td>Identify or re-engage family members to support/supervise adherence.</td>
</tr>
<tr>
<td></td>
<td>2. Review pharmacy records</td>
<td>Establish fixed daily times and routines for medication administration.</td>
</tr>
<tr>
<td></td>
<td>3. Observe medication administration</td>
<td>Avoid confusion with drug names by explaining that drug therapies have</td>
</tr>
<tr>
<td></td>
<td>4. Conduct psychosocial assessment</td>
<td>generic names and trade names, and many agents are coformulated under a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>third or fourth name.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Explore opportunities for facility or home-based directly observed therapy.</td>
</tr>
<tr>
<td></td>
<td>1. Take 24-hour or 7-day recall</td>
<td>Simplify medication regimen if feasible.</td>
</tr>
<tr>
<td></td>
<td>2. Get description of:</td>
<td>Substitute new agents if single ARV is poorly tolerated.</td>
</tr>
<tr>
<td></td>
<td>○ WHO gives medication</td>
<td>Consider gastric tube placement to facilitate adherence.</td>
</tr>
<tr>
<td></td>
<td>○ WHAT is given (names, doses)</td>
<td>Consider directly observed therapy (DOT).</td>
</tr>
<tr>
<td></td>
<td>○ WHERE medications are kept, administered</td>
<td>Use tools to simplify administration (pill boxes, reminders including</td>
</tr>
<tr>
<td></td>
<td>○ WHEN they are taken/given</td>
<td>alarms, integrated medication packaging for AM or PM dosing, others).</td>
</tr>
<tr>
<td></td>
<td>3. Have open-ended discussion of experiences taking/giving medications</td>
<td>Suggest relaxation techniques.</td>
</tr>
<tr>
<td></td>
<td>○ Where medications are kept, administered</td>
<td>Address competing needs through appropriate social services.</td>
</tr>
<tr>
<td></td>
<td>○ WHEN they are taken/given</td>
<td>Address and treat concomitant mental illness and behavioral disorders. Initiate</td>
</tr>
<tr>
<td></td>
<td>○ Have open-ended discussion of experiences taking/giving medications and barriers/challenges</td>
<td>disclosure discussions with family/child.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider need for child protection services and alternate care settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>when necessary.</td>
</tr>
<tr>
<td></td>
<td>1. Interview child and caretaker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Review pharmacy records</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Observe medication administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Conduct psychosocial assessment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Take 24-hour or 7-day recall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Get description of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ WHO gives medication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ WHAT is given (names, doses)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ WHERE medications are kept, administered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ WHEN they are taken/given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Have open-ended discussion of experiences taking/giving medications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ Where medications are kept, administered</td>
<td></td>
</tr>
<tr>
<td></td>
<td>○ WHEN they are taken/given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Recalculate doses for individual medications using weight or body</td>
<td>Adjust drug doses.</td>
</tr>
<tr>
<td></td>
<td>surface area.</td>
<td>Discontinue or substitute competing medications.</td>
</tr>
<tr>
<td></td>
<td>2. Identify concomitant medications including prescription, over-the-counter, and recreational substances; assess for drug-drug interactions.</td>
<td>Reinforce applicable food restrictions.</td>
</tr>
<tr>
<td></td>
<td>3. Consider drug levels for specific antiretroviral drugs (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure).</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacokinetics and Dosing</strong></td>
<td>1. Perform genotypic and phenotypic resistance assays (see Antiretroviral Drug-Resistance Testing).</td>
<td></td>
</tr>
</tbody>
</table>
Table 20. Options for Regimens with at Least Two Fully Active Agents Following Failure of Antiretroviral Regimen with Evidence for Viral Resistance to Therapy with Goal of Virologic Suppression*

<table>
<thead>
<tr>
<th>Prior Regimen</th>
<th>Recommended Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 NRTIs + NNRTI</td>
<td>• 2 NRTIs (based on resistance testing) + PI</td>
</tr>
<tr>
<td>2 NRTIs + PI</td>
<td>• 2 NRTIs (based on resistance testing) + NNRTI</td>
</tr>
<tr>
<td></td>
<td>• 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir boosting, based on resistance testing)</td>
</tr>
<tr>
<td></td>
<td>• NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir boosting, based on resistance testing)</td>
</tr>
<tr>
<td>3 NRTIs</td>
<td>• 2 NRTIs (based on resistance testing) + (NNRTI or PI)</td>
</tr>
<tr>
<td></td>
<td>• NRTI(s) (based on resistance testing) + (NNRTI + PI)</td>
</tr>
<tr>
<td>Failed regimens including NRTI, NNRTI, PI</td>
<td>• &gt;1 NRTI (based on resistance testing) + a newer PI (with low-dose ritonavir boosting, based on resistance testing)</td>
</tr>
<tr>
<td></td>
<td>• &gt;1 NRTI + dual-boosted PI (LPV/r + SQV, LPV/r + ATV)</td>
</tr>
<tr>
<td></td>
<td>(consider adding either one or more of T-20, ETR, or an integrase inhibitor)</td>
</tr>
<tr>
<td></td>
<td>• NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + ETR</td>
</tr>
<tr>
<td></td>
<td>• NRTI(s) + ritonavir-boosted, potent PI (based upon resistance testing) + T-20 and/or CCR5 antagonist and/or integrase inhibitor</td>
</tr>
<tr>
<td></td>
<td>• If patient refuses PI and/or ritonavir boosting: NRTI(s) + T-20 and/or integrase inhibitor and/or CCR5 antagonist</td>
</tr>
</tbody>
</table>

* Antiretroviral regimens should be chosen based on treatment history and drug-resistance testing to optimize antiretroviral drug effectiveness in the second regimen. This is particularly important in selecting NRTI components of an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable, potent virologic suppression.

**Key to Abbreviations:** T-20 = enfuvirtide, ATV = atazanavir, ETR = etravirine, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, SQV = saquinavir
Table 21. Suggested Minimum Target Trough Concentrations*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamprenavir (measured as amprenavir concentration)</td>
<td>400</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>150</td>
</tr>
<tr>
<td>Indinavir</td>
<td>100</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>1,000</td>
</tr>
<tr>
<td>Nelfinavir (Measurable active [M8] metabolite)</td>
<td>800</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>100–250</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1,000</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>3,000</td>
</tr>
</tbody>
</table>

**Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>20,500</td>
</tr>
</tbody>
</table>


http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf

References