Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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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 ARV agents in infants, children, and adolescents (through mid-puberty) living with HIV in the United States.</td>
</tr>
<tr>
<td>Panel Members</td>
<td>The Panel is composed of approximately 35 voting members who have expertise in 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 (e.g., parents and caregivers of children and youth living with HIV). 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). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, ex officio member of the Panel. 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 in the Panel Roster.</td>
</tr>
<tr>
<td>Financial Disclosure</td>
<td>All members of the Panel submit an annual financial disclosure statement in writing, reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDSInfo website (<a href="http://aidsinfo.nih.gov">http://aidsinfo.nih.gov</a>).</td>
</tr>
<tr>
<td>Users of the Guidelines</td>
<td>Providers of care to infants, children, and adolescents living with HIV in the United States</td>
</tr>
<tr>
<td>Developer</td>
<td>Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of OARAC</td>
</tr>
<tr>
<td>Funding Source</td>
<td>Office of AIDS Research, NIH and HRSA</td>
</tr>
<tr>
<td>Evidence Collection</td>
<td>A standardized review of recent, relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. The Panel may occasionally use unpublished data to revise the guidelines, particularly when the new information relates to dosing or patient safety. These data come from presentations at major conferences or from the FDA and/or drug manufacturers.</td>
</tr>
<tr>
<td>Recommendation Grading</td>
<td>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 recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.</td>
</tr>
<tr>
<td>Other Guidelines</td>
<td>These guidelines focus on infants, children, and adolescents in early puberty (SMR I–III) living with HIV. Guidance for treatment of adolescents in late puberty (SMR IV–V) is provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of ART in pregnant women with HIV infection (including maternal and infant interventions for prevention of perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV infection, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDSInfo website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>).</td>
</tr>
<tr>
<td>Update Plan</td>
<td>The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). 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. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDSInfo website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed, with updates as appropriate, at least once a year.</td>
</tr>
<tr>
<td>Public Comments</td>
<td>A 2-week public comment period follows release of the updated guidelines on the AIDSInfo website. 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 <a href="mailto:contactus@aidsinfo.nih.gov">contactus@aidsinfo.nih.gov</a>.</td>
</tr>
</tbody>
</table>

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### 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(^a) 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 plus accompanying data in children(^a) 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(^a) 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 plus accompanying data in children(^a) 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>

\(^a\) Studies that include children or children and adolescents, but not studies limited to post-pubertal adolescents
Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Entry Into Care</th>
<th>Pre-Therapy</th>
<th>ART Initiation</th>
<th>Weeks 1–2 on Therapy</th>
<th>Weeks 2–4 on Therapy</th>
<th>Every 3–4 Months</th>
<th>Only Required Every 6–12 Months</th>
<th>ARV Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Adherence Evaluation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CD4 Count</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Plasma Viral Load</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Resistance Testing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CBC with Differential</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Chemistries</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Lipid Panel</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Random Plasma Glucose</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Urinalysis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hepatitis B Screening</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*See text for details on recommended laboratory tests to obtain.

* Readiness for ARV adherence is assessed prior to starting ART. If abacavir is being considered as part of the regimen, send HLA-B*5701 testing prior to initiation of that ARV and choose an alternative ARV if HLA-B*5701 is positive (see [Abacavir](https://aidsinfo.nih.gov/guidelines) in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if not already performed (see [Antiretroviral Drug-Resistance Testing](https://aidsinfo.nih.gov/guidelines) in the Adult and Adolescent Antiretroviral Guidelines). Send tests appropriate to the toxicities expected from each patient's ART regimen and history (see text).

* If ART is initiated within 30 to 90 days of a pre-therapy lab result, repeat testing may not be necessary.

* CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell values well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

* If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

* Chemistries refer to a comprehensive metabolic panel.

* Random plasma glucose collected in a gray top tube.

* Recommended when considering starting ARV drugs with activity against hepatitis B, specifically lamivudine-, emtricitabine-, and tenofovir-containing regimens.

* Recommended only when individual previously demonstrated no immunity to hepatitis B.

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; CBC = complete blood count; CD4 = CD4 T lymphocyte; TDF = tenofovir disoproxil fumarate
### Table 4. Primary, FDA-Approved Assays to Monitor Viral Load

<table>
<thead>
<tr>
<th>Assay</th>
<th>Abbott Real Time</th>
<th>NucliSens EasyQ v 2.0</th>
<th>COBAS Ampliprep/TagMan v 2.0</th>
<th>Versant v 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method</td>
<td>Real-time RT-PCR</td>
<td>Real-time NASBA</td>
<td>Real-time RT-PCR</td>
<td>Real-time RT-PCR</td>
</tr>
<tr>
<td>Dynamic Range (copies/mL)</td>
<td>40–10⁷</td>
<td>25–10⁷</td>
<td>20–10⁷</td>
<td>37–11x10⁷</td>
</tr>
<tr>
<td>Specimen volume*</td>
<td>0.2–1 mL</td>
<td>0.1–1 mL</td>
<td>1 mL</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Abbott</td>
<td>bioMerieux</td>
<td>Roche</td>
<td>Siemens</td>
</tr>
</tbody>
</table>

* Smaller volumes for children can be accommodated.

**Key to Acronyms:** FDA = Food and Drug Administration; NASBA = nucleic acid sequence-based amplification; RT-PCR = reverse transcription polymerase chain reaction

### Table 5. HIV Infection Stagea Based on Age-Specific CD4 Cell Count or Percentage

<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt;1 Year Cells/µL</th>
<th>%</th>
<th>1 to &lt;6 Years Cells/µL</th>
<th>%</th>
<th>≥6 Years Cells/µL</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥1,500</td>
<td>≥34</td>
<td>≥1,000</td>
<td>≥30</td>
<td>≥500</td>
<td>≥26</td>
</tr>
<tr>
<td>2</td>
<td>750–1,499</td>
<td>26–33</td>
<td>500–999</td>
<td>22–29</td>
<td>200–499</td>
<td>14–25</td>
</tr>
<tr>
<td>3</td>
<td>&lt;750</td>
<td>&lt;26</td>
<td>&lt;500</td>
<td>&lt;22</td>
<td>&lt;200</td>
<td>&lt;14</td>
</tr>
</tbody>
</table>

* The stage is based primarily on the CD4 cell count; the CD4 cell count takes precedence over the CD4 percentage, and the percentage is considered only if the count is missing. If a Stage 3-defining opportunistic illness has been diagnosed (Table 6), then the stage is 3 regardless of CD4 test results.


**Key to Acronyms:** CD4 = CD4 T lymphocyte
### Mild HIV-Related Symptoms

Children with 2 or more of the conditions listed, but none of the conditions listed in Moderate Symptoms category:

- Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media

### Moderate HIV-Related Symptoms

- Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000/µL [<1.0 × 10⁹/L]), and/or thrombocytopenia (platelet count <100 × 10⁹/µL [<100 × 10⁹/L]) persisting for ≥30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children aged >6 months
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month
- Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month
- Varicella, disseminated (complicated chickenpox)
### Stage-3-Defining Opportunistic Illnesses in HIV Infection

- **Bacterial infections, multiple or recurrent**<sup>a</sup>
- **Candidiasis of bronchi, trachea, or lungs**
- **Candidiasis of esophagus**
- **Cervical cancer, invasive**<sup>b</sup>
- **Coccidioidomycosis, disseminated or extrapulmonary**
- **Cryptococcosis, extrapulmonary**
- **Cryptosporidiosis, chronic intestinal (>1 month duration)**
- **Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month**
- **Cytomegalovirus retinitis (with loss of vision)**
- **Encephalopathy attributed to HIV**<sup>c</sup>
- **HSV: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)**
- **Histoplasmosis, disseminated or extrapulmonary**
- **Isosporiasis, chronic intestinal (>1 month duration)**
- **Kaposi sarcoma**
- **Lymphoma, Burkitt (or equivalent term)**
- **Lymphoma, immunoblastic (or equivalent term)**
- **Lymphoma, primary, of brain**
- **Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary**
- **Mycobacterium tuberculosis of any site, pulmonary, disseminated, or extrapulmonary**
- **Mycobacterium, other species or unidentified species, disseminated or extrapulmonary**
- **Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia**
- **Pneumonia, recurrent**<sup>b</sup>
- **Progressive multifocal leukoencephalopathy**
- **Salmonella septicemia, recurrent**
- **Toxoplasmosis of brain, onset at age >1 month**
- **Wasting syndrome attributed to HIV**<sup>c</sup>

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<sup>a</sup> Only among children aged <6 years.

<sup>b</sup> Only among adults, adolescents, and children aged ≥6 years.

<sup>c</sup> Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

- Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).

Modified from:

- Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).
Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

An ART regimen for treatment-naive children generally contains one NNRTI or one PI boosted with RTV or COBI or one INSTI plus a two-NRTI backbone. Preferred regimens are designated based on efficacy, ease of administration, and acceptable toxicity. Alternative regimens have also demonstrated efficacy, but have more limited experience in children or less favorable ease of administration than Preferred regimens. Regimens should be individualized based on the advantages and disadvantages of each combination (see Table 8).

Children who are receiving effective and tolerable ART regimens can continue with those regimens as they age, even if the combinations they are receiving are no longer Preferred regimens.

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Age</th>
<th>Regimens</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants, Birth to Age &lt;14 Days&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2 NRTIs plus NVP</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus RAL</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥14 Days to &lt;3 Years</td>
<td>2 NRTIs plus LPV/r</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2 NRTIs plus ATV/r</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus twice-daily DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2 NRTIs plus ATV/r</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus DTG&lt;sup&gt;e&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 1–3</td>
<td>2 NRTIs plus ATV/r</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus DTG&lt;sup&gt;e&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus once-daily DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 NRTIs plus EVG/COBI&lt;sup&gt;f&lt;/sup&gt;</td>
<td>FDCs available</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 4 or 5</td>
<td>Refer to the Adult and Adolescent Guidelines</td>
<td>No</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Alternative Regimens</th>
<th>Age</th>
<th>Regimens</th>
<th>Fixed-Dose Combination Available</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children Aged &gt;14 Days to &lt;3 Years</td>
<td>2 NRTIs plus NVP&lt;sup&gt;g&lt;/sup&gt;</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Children Aged ≥3 Months to &lt;3 Years and Weighing ≥10 kg</td>
<td>2 NRTIs plus ATV/r</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

<table>
<thead>
<tr>
<th>Age</th>
<th>Regimens</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus LPV/r</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2 NRTIs plus twice-daily DRV/r&lt;sup&gt;†&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus EVG/COBI</td>
<td>FDCs available</td>
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<tr>
<td></td>
<td>2 NRTIs plus LPV/r</td>
<td>No</td>
</tr>
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<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 1–3</td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RPV&lt;sup&gt;i&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
</tbody>
</table>

Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs

<table>
<thead>
<tr>
<th>Age</th>
<th>2-NRTI Backbone Options</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, Birth to Age &lt;3 Months</td>
<td>ZDV plus (3TC or FTC)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥3 Months to &lt;6 Years</td>
<td>ABC plus (3TC or FTC)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td></td>
<td>ZDV plus (3TC or FTC)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥6 Years</td>
<td>ABC plus (3TC or FTC)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>and SMR 1–3</td>
<td>FTC/TAF&lt;sup&gt;l&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 4 or 5</td>
<td>Refer to the Adult and Adolescent Guidelines</td>
<td>No</td>
</tr>
</tbody>
</table>

Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs

<table>
<thead>
<tr>
<th>Age</th>
<th>2-NRTI Backbone Options</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥3 Months</td>
<td>ZDV plus ABC</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥2 Years to 12 Years</td>
<td>TDF plus (3TC or FTC)&lt;sup&gt;m&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥6 Years</td>
<td>ZDV plus (3TC or FTC)&lt;sup&gt;m&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>and SMR 1–3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are Preferred agents because they are the only options with dosing information available for this age group. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Clinicians should consult an expert in pediatric HIV infection. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in Antiretroviral Management of Newborns. A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks postmenstrual age (the span of time between the first day of the mother’s last menstrual period and birth, plus the time elapsed after birth), based on infant genotype and better outcomes of LPV/r than NVP in children aged <3 years. Data are very limited on the clinical outcomes of using RAL in infants and children aged <2 years.

<sup>b</sup> LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and postnatal age ≥14 days.

<sup>c</sup> RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children from birth to age 2 years.

<sup>d</sup> DRV once daily should not be used in children aged <12 years or weighing <40 kg. DRV once daily should also not be used if any one of the following resistance-associated substitutions are present: V11L, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is an Alternative recommendation for children aged ≥6 years to <12 years because there are options that can be administered once daily. It is Preferred for adolescents aged ≥12 years who are not sexually mature (SMR 1–3) where once-daily administration is possible.

<sup>e</sup> DTG is recommended only for children and adolescents weighing ≥30 kg. An FDC tablet containing ABC/DTG/3TC (Triumeq) is available.

<sup>f</sup> EVG is currently recommended only in FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as Preferred for children...
Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued
and adolescents weighing ≥35 kg and as Alternative for children aged ≥6 years and weighing ≥25 kg.

9 NVP should not be used in postpubertal girls with CD4 cell counts >250/mm³, unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged ≥15 days.

10 EFV is licensed for use in children aged ≥3 months and weighing ≥3.5 kg, but it is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years. An FDC tablet containing EFV/FTC/TDF (Atripla) is available.

11 RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL. FDC tablets containing FTC/RPV/TAI (Odefsey) and FTC/RPV/TDF (Complera) are available.

12 An FDC containing 3TC/ZDV (Combivir and generic) is available.

13 An FDC containing ABC/3TC (Epzicom and generic) is available.

14 An FDC containing FTC/TAF is available. FTC/TAF is FDA-approved for children weighing ≥25 kg when used in the single-tablet regimen EVG/COBI/FTC/TAF or as TAF/FTC in combination with an NNRTI or INSTI. There is insufficient data to recommend use of FTC/TAF in combination with a boosted PI in children weighing <35 kg. For children and adolescents weighing ≥35 kg, TAF can be used in the single-tablet regimen EVG/COBI/FTC/TAF, or as FTC/TAF in combination with an NNRTI, an INSTI, or a boosted PI.

15 An FDC containing FTC/TDF (Truvada) is available.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; COBI=cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children* (page 1 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| INSTIs In Alphabetical Order | All INSTIs | INSTI Class Advantages:  
- Susceptibility of HIV to a new class of ARV drugs  
- Few drug-drug interactions  
- Well-tolerated | INSTI Class Disadvantages:  
- Limited data on pediatric dosing or safety |
| DTG |  
- Once-daily administration  
- Can give with food  
- Available in an FDC tablet containing ABC/DTG/3TC (Triumeq) in a single, but large, tablet  
- Single-agent DTG pills are available in several dosages and are small in size. |  
- Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing  
- CNS side effects, particularly sleep disturbances |
| EVG |  
- Once-daily administration  
- Available in the following FDC tablets: EVG/COBI/FTC/TDF (Stribild) and EVG/COBI/FTC/TAF (Genvoya) |  
- COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4).  
- COBI inhibits tubular secretion of creatinine and may result in increased serum creatinine but normal glomerular clearance. |
| RAL |  
- Can give with food  
- Available in tablet, chewable tablet, and powder formulations  
- Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥50 kg. |  
- Potential for rare systemic allergic reaction or hepatitis  
- Powder formulation requires a multistep preparation before administration. |
Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children* (page 2 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong>&lt;br&gt;In Alphabetical Order</td>
<td>All NNRTIs</td>
<td>NNRTI Class Advantages:&lt;br&gt;- Long half-life&lt;br&gt;- Less dyslipidemia and fat maldistribution than PIs&lt;br&gt;- PI-sparing&lt;br&gt;- Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens</td>
<td>NNRTI Class Disadvantages:&lt;br&gt;- Single mutation can confer resistance, with cross-resistance between EFV and NVP&lt;br&gt;- Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP)&lt;br&gt;- Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)</td>
</tr>
<tr>
<td><strong>EFV</strong></td>
<td>• Once-daily administration&lt;br&gt;- Available in the FDC EFV/FTC/TDF (Atripla)&lt;br&gt;- Potent ARV activity&lt;br&gt;- Can give with food (but avoid high-fat meals)&lt;br&gt;- Capsules can be opened and added to food</td>
<td>• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects)&lt;br&gt;- Rash (generally mild)&lt;br&gt;- No commercially available liquid&lt;br&gt;- Limited data on dosing for children aged &lt;3 years&lt;br&gt;- No data on dosing for children aged &lt;3 months</td>
<td></td>
</tr>
<tr>
<td><strong>NVP</strong></td>
<td>• Liquid formulation available&lt;br&gt;- Dosing information for young infants available&lt;br&gt;- Can give with food&lt;br&gt;- Extended-release formulation is available that allows for once-daily dosing in older children.</td>
<td>• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen&lt;br&gt;- Higher incidence of rash/HSR than other NNRTIs&lt;br&gt;- Higher rates of serious hepatic toxicity than EFV&lt;br&gt;- Decreased virologic response compared with EFV&lt;br&gt;- Twice-daily dosing necessary in children with BSA &lt;0.58 m²</td>
<td></td>
</tr>
<tr>
<td><strong>RPV</strong></td>
<td>• Once-daily dosing&lt;br&gt;- Available in the following 1-pill-daily, FDC tablets: FTC/RPV/TDF (Complera) and FTC/RPV/TAF (Odefsey)</td>
<td>• Should not use in patients with HIV viral load &gt;100,000 copies/mL&lt;br&gt;- Low barrier for resistance</td>
<td></td>
</tr>
<tr>
<td><strong>PIs</strong>&lt;br&gt;In Alphabetical Order</td>
<td>All PIs</td>
<td>PI Class Advantages:&lt;br&gt;- NNRTI-sparing&lt;br&gt;- Clinical, virologic, and immunologic efficacy are well-documented.&lt;br&gt;- Resistance to PIs requires multiple mutations&lt;br&gt;- When combined with a dual-NRTI backbone, a regimen containing a PI targets HIV at 2 steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.</td>
<td>PI Class Disadvantages:&lt;br&gt;- Metabolic complications, including dyslipidemia, fat maldistribution, insulin resistance&lt;br&gt;- Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4)&lt;br&gt;- Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations&lt;br&gt;- Poor palatability of liquid preparations, which may affect adherence to treatment regimen&lt;br&gt;- Most PIs require RTV boosting, resulting in associated drug interactions.</td>
</tr>
<tr>
<td>ARV Class</td>
<td>ARV Agent(s)</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>------------</td>
<td>--------------</td>
</tr>
</tbody>
</table>
| **PIs** In Alphabetical Order, continued | **Boosted ATV** | • Once-daily dosing  
• Powder formulation available  
• ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).  
• **ATV requires a boosting agent. ATV/COBI is available as an FDC tablet (Evotaz), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of ATP/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for ATV that is FDA-approved for use in children.**  
• No liquid formulation  
• Food effect (should be administered with food)  
• Indirect hyperbilirubinemia is common, but asymptomatic  
• Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG)  
• RTV component associated with a large number of drug interactions | |
| Boosted | **DRV** | • Can be used once daily in children aged ≥12 years  
• Liquid formulation available  
• **DRV requires a boosting agent. DRV/COBI is available as an FDC tablet (Prezco benix), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of DRV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for DRV that is FDA-approved for use in children.**  
• Pediatric pill burden high with current tablet dose formulations  
• Food effect (should be administered with food)  
• **Must be boosted** to achieve adequate plasma concentrations  
• Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown. | |
| **LPV/r** | | • LPV only available coformulated with RTV in liquid and tablet formulations  
• Tablets can be given without regard to food, but may be better tolerated when taken with meal or snack. | • Poor palatability of liquid formulation (bitter taste), although palatability of combination is better than RTV alone  
• Food effect (liquid formulation should be administered with food)  
• RTV component is associated with large number of drug interactions  
• Should not be administered to neonates before a postmenstrual age (the span of time between the first day of the mother’s last menstrual period and birth, plus the time elapsed after birth) of 42 weeks and a postnatal age ≥14 days  
• Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG) |
| **Dual-NRTI Backbones** In Alphabetical Order | **ABC plus (3TC or FTC)** | • Palatable liquid formulations  
• Can give with food.  
• **ABC and 3TC are available in the following FDC tablets: ABC/3TC (Epzicom and generic; for older/larger patients) and ABC/DTG/3TC (Triumeq; a single, large tablet).**  
• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. | |
| | **FTC/TAF for children aged ≥6 years** | • Once-daily dosing  
• Small tablet size  
• Less TFV-associated renal and bone toxicity with TAF compared to TDF in adults  
• FTC and TAF are available in the following FDC tablets: FTC/TAF (Descovy), EVG/COBI/FTC/TAF (Genvoya), and FTC/RPV/TAF (Odefsey) | • **Limited data in children**  
• Increased lipids |
### Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children* (page 4 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Dual-NRTI Backbones    | TDF plus (3TC or FTC) for adolescents  | • Once-daily dosing for TDF  
• Resistance is slow to develop  
• Less mitochondrial toxicity than other NRTIs  
• Can give with food  
• Available as reduced-strength tablets and oral powder for use in younger children  
• FTC and TDF are available in the following FDC tablets: FTC/TDF (Truvada; available in multiple dosages), EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and FTC/RPV/TDF (Complera)  | • Limited pediatric experience  
• Potential bone and renal toxicity; toxicity may be less in post-pubertal children  
• Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV. |
|                        | with SMR 4 or 5                         |                                                                                                                                                                                                           |                                                                                                  |
|                        | ZDV plus (3TC or FTC)                  | • Extensive pediatric experience  
• ZDV and 3TC are coformulated as single pill (Combivir and generic) for older/larger patients.  
• Palatable liquid formulations  
• Can give with food  
• FTC is available as a palatable liquid formulation administered once daily. | • Bone marrow suppression with ZDV  
• Lipoatrophy with ZDV                                                                                                               |
|                        | ZDV plus ABC                           | • Palatable liquid formulations  
• Can give with food                                                                                                                                                                                     | • Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment  
• Bone marrow suppression and lipoatrophy with ZDV                                                                                       |

* See Appendix A: Pediatric Antiretroviral Drug Information and Table 7, Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios in the Adult and Adolescent Guidelines for more information.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; CYP = cytochrome P; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine
**Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children**

<table>
<thead>
<tr>
<th>Regimen or ARV Component</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unboosted <strong>ATV</strong>-containing regimens in children</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td><strong>DRV</strong>-based regimens once daily in children aged ≥3 to 12 years</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Unboosted <strong>DRV</strong></td>
<td>Use without ritonavir has not been studied</td>
</tr>
<tr>
<td>Dual (full-dose) PI regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Potencial for added toxicities</td>
<td></td>
</tr>
<tr>
<td>Dual-NRTI combination of <strong>ABC plus TDF</strong></td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td><strong>EFV</strong>-based regimens for children aged &lt;3 years</td>
<td>Appropriate dose not determined</td>
</tr>
<tr>
<td><strong>T-20</strong>-containing regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Injectable preparation</td>
<td></td>
</tr>
<tr>
<td><strong>ETR</strong>-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td><strong>FPV</strong>-based regimens</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td>Medication burden</td>
<td></td>
</tr>
<tr>
<td><strong>IDV</strong>-based regimens</td>
<td>Renal toxicities</td>
</tr>
<tr>
<td><strong>LPV/r</strong> dosed once daily</td>
<td>Reduced drug exposure</td>
</tr>
<tr>
<td><strong>MVC</strong>-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td><strong>NFV</strong>-based regimens</td>
<td>Variable PK</td>
</tr>
<tr>
<td>Appropriate dose not determined in young infants</td>
<td></td>
</tr>
<tr>
<td>Regimens containing only NRTIs</td>
<td>Inferior virologic efficacy</td>
</tr>
<tr>
<td>Regimens containing 3 drug classes</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Full-dose <strong>RTV</strong> or use of <strong>RTV</strong> as the sole PI</td>
<td>GI intolerance</td>
</tr>
<tr>
<td>Metabolic toxicity</td>
<td></td>
</tr>
<tr>
<td>Regimens containing 3 NRTIs and 1 NNRTI</td>
<td>Added cost and complexity outweighs any benefit</td>
</tr>
<tr>
<td><strong>SQV</strong>-based regimens</td>
<td>Limited dosing and outcome data</td>
</tr>
<tr>
<td><strong>TDF</strong>-containing regimens in children aged &lt;2 years</td>
<td>Potential bone toxicity</td>
</tr>
<tr>
<td>Appropriate dose has yet to be determined</td>
<td></td>
</tr>
<tr>
<td><strong>TPV</strong>-based regimens</td>
<td>Increased dose of <strong>RTV</strong> for boosting</td>
</tr>
<tr>
<td>Reported cases of intracranial hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

**Key to Acronyms:** **ABC** = abacavir; **ARV** = antiretroviral; **ATV** = atazanavir; **DRV** = darunavir; **EFV** = efavirenz; **ETR** = etravirine; **FPV** = fosamprenavir; **GI** = gastrointestinal; **IDV** = indinavir; **LPV/r** = lopinavir/ritonavir; **MVC** = maraviroc; **NFV** = nelfinavir; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor; **PK** = pharmacokinetics; **RTV** = ritonavir; **SQV** = saquinavir; **T-20** = enfuvirtide; **TDF** = tenofovir disoproxil fumarate; **TPV** = tipranavir
Table 10. ART Regimens or Components Never Recommended for Treatment of HIV Infection in Children

<table>
<thead>
<tr>
<th>ART Regimens Never Recommended for Children</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
</table>
| 1 ARV Drug Alone (Monotherapy)             | • Rapid development of resistance  
• Inferior antiviral activity compared to combinations that include ≥3 ARV drugs  
• Monotherapy “holding” regimens are associated with more rapid CD4 declines than non-suppressive ART | • Infants with perinatal HIV exposure and negative virologic tests who are receiving 4 to 6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV |
| 2 NRTIs Alone                              | • Rapid development of resistance  
• Inferior antiviral activity compared to combinations that include ≥3 ARV drugs | • Not recommended for initial therapy.  
• For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment. |
| TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen | • High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults | • No exceptions |
| TDF plus ddI plus (3TC or FTC) as a Triple-NRTI Regimen | • High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults | • No exceptions |

<table>
<thead>
<tr>
<th>ARV Components Never Recommended as Part of an ARV Regimen for Children</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
</table>
| ddI and d4T, Individually or Co-Administered                          | • Increased toxicities  
• ddI plus d4T is contraindicated | • No exceptions |
| ATV plus IDV                                                            | • Potential additive hyperbilirubinemia | • No exceptions |
| Dual-NRTI Combinations                                                 | • Enhanced toxicity | • No exceptions |
| Dual-NRTI Combinations:                                                | • Similar resistance profile and no additive benefit | • No exceptions |
| • 3TC plus FTC                                                         |                        | |
| • d4T plus ZDV                                                         | • Antagonistic effect on HIV | • No exceptions |
| NVP as Initial Therapy in Adolescent Girls with CD4 Counts >250 cells/mm³ or Adolescent Boys with CD4 Counts >400 cells/mm³ | • Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups | • Only if benefit clearly outweighs risk |
| Unboosted SQV, DRV, or TPV                                             | • Poor oral bioavailability  
• Inferior virologic activity compared with other PIs | • No exceptions |

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; DRV = darunavir; FTC = emtricitabine; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ZDV = zidovudine
### Table 11. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (888-448-8765).

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Neonatal ARV Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk of Perinatal HIV Transmission</td>
<td>• Mothers who received ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence</td>
<td>ZDV for 4 weeks</td>
</tr>
</tbody>
</table>
| Higher Risk of Perinatal HIV Transmission | • Mothers who received neither antepartum nor intrapartum ARV drugs  
• Mothers who received only intrapartum ARV drugs  
• Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal  
• Mothers with acute or primary HIV infection during pregnancy or breastfeeding (In which case, the mother should discontinue breastfeeding)  
| 2-drug ARV prophylaxis ([NICHD-HPTN 040/PACTG 1043 regimen](https://aidsinfo.nih.gov/guidelines)) with 6 weeks ZDV and 3 doses of NVP (prophylactic dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose)  
| or  
| Empiric HIV therapy using either ZDV, 3TC, and NVP (treatment dosage) or ZDV, 3TC, and RAL administered from birth to age 6 weeks.  
| Presumed Newborn HIV Exposure        | • Mothers with unknown HIV status who test HIV positive at delivery or postpartum or whose newborns have a positive HIV antibody test                                                                           | ARV management as above (for higher risk of perinatal HIV transmission)                 |
|                                         | Infant ARVs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV.                                                                                           |                                                                                        |
| Newborn with HIV  
|  | • Positive newborn HIV virologic test/NAT  
|  | 3-drug ARV regimen using treatment dosages                                                                                                             |                                                                                        |

* See text for evidence supporting a 2-drug ARV prophylaxis regimen and empiric HIV therapy.

* See the Intrapartum care section for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with an elevated viral load at delivery.

* Most Panel members would opt to administer empiric HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for in utero transmission. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.

* The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when a birth NAT returns negative, while others would continue empiric HIV therapy for infants at highest risk of HIV acquisition for 6 weeks. In all cases, ZDV should be continued for 6 weeks. It is recommended that providers consult with an expert in pediatric HIV infection to determine therapy duration based on case-specific risk factors and interim HIV NAT results.

* Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given low likelihood of a false-positive HIV NAT.

**Note:** ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 12 for dosing specifics.

**Key to Acronyms:** 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; the Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine
### Table 12. Antiretroviral Dosing Recommendations for Newborns

#### Newborns at Low Risk of Perinatal HIV Transmission

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>ZDV administered for 4 weeks</td>
</tr>
</tbody>
</table>

#### Newborns at Higher Risk of Perinatal HIV Transmission

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-drug ARV prophylaxis with ZDV and 3 doses of NVP (NICHD-HPTN 040/PACTG 1043 regimen), or</td>
<td>ZDV administered for 6 weeks; 3 doses of NVP during the first week of life</td>
</tr>
<tr>
<td>Empiric HIV therapy with ZDV/3TC/NVP, or</td>
<td>ZDV administered for 6 weeks; 3TC and NVP administered for 2–6 weeks, up to 6 weeks of age</td>
</tr>
<tr>
<td>Empiric HIV therapy with ZDV/3TC/RAL</td>
<td>ZDV administered for 6 weeks; 3TC and RAL administered for 2–6 weeks, up to 6 weeks of age</td>
</tr>
</tbody>
</table>

#### Newborns with HIV Infection

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Recommended Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV therapy with ZDV/3TC/NVP, or</td>
<td>Lifelong therapy</td>
</tr>
<tr>
<td>HIV therapy with ZDV/3TC/RAL</td>
<td>Lifelong therapy</td>
</tr>
</tbody>
</table>

### Indication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Risk Prophylaxis</th>
<th>Higher Risk Prophylaxis: 2-Drug</th>
<th>Higher Risk Prophylaxis: Empiric and HIV Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>Note: For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|      | ≥35 Weeks Gestation at Birth:  
  • ZDV 4 mg/kg/dose orally twice daily |
|      | Simplified Weight-Band Dosing for Newborns ≥35 Weeks Gestation at Birth: |
|      | Weight Band (kg) | Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily |
|      | 2 to <3 kg | 1 mL |
|      | 3 to <4 kg | 1.5 mL |
|      | 4 to <5 kg | 2 mL |
|      | ≥30 to <35 Weeks Gestation at Birth  
  Birth to Age 2 Weeks:  
  • ZDV 2 mg/kg/dose orally twice daily  
  Age 2 Weeks to 4–6 Weeks:  
  • ZDV 3 mg/kg/dose orally twice daily |
|      | ≤30 to <35 Weeks Gestation at Birth  
  Birth to Age 2 Weeks:  
  • ZDV 2 mg/kg/dose orally twice daily  
  Age 2 Weeks to 6–8 Weeks:  
  • ZDV 3 mg/kg/dose orally twice daily  
  Age >6–8 Weeks:  
  • ZDV 12 mg/kg/dose orally twice daily |
|      | <30 Weeks Gestation at Birth  
  Birth to Age 4–6 Weeks:  
  • ZDV 2 mg/kg/dose orally twice daily |
|      | ≤30 to <35 Weeks Gestation at Birth  
  Birth to Age 2 Weeks:  
  • ZDV 2 mg/kg/dose orally twice daily  
  Age 2 Weeks to 6–8 Weeks:  
  • ZDV 3 mg/kg/dose orally twice daily  
  Age >6–8 Weeks:  
  • ZDV 12 mg/kg/dose orally twice daily |
|      | <30 Weeks Gestation at Birth  
  Birth to Age 4–6 Weeks:  
  • ZDV 2 mg/kg/dose orally twice daily |
|      | ≤32 Weeks Gestation at Birth  
  Birth to Age 4 Weeks:  
  • ZDV 2 mg/kg/dose orally twice daily  
  Age 4 to 8–10 Weeks:  
  • ZDV 3 mg/kg/dose orally twice daily  
  Aged >8–10 Weeks:  
  • ZDV 12 mg/kg/dose orally twice daily |
| 3TC  | N/A | N/A | =32 Weeks Gestation at Birth  
  Birth to Age 4 Weeks:  
  • 3TC 2 mg/kg/dose orally twice daily  
  Age >4 Weeks:  
  • 3TC 4 mg/kg/dose orally twice daily |
### Table 12. Antiretroviral Dosing Recommendations for Newborns (page 2 of 2)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Low Risk Prophylaxis</th>
<th>Higher Risk Prophylaxis: 2-Drug</th>
<th>Higher Risk Prophylaxis: Empiric and HIV Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>N/A</td>
<td>≥32 Weeks Gestation at Birth:</td>
<td>≥37 Weeks Gestation at Birth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NVP in 3 doses given</td>
<td>Birth to Age 4 Weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Within 48 hours of birth,</td>
<td>• NVP 6 mg/kg/dose orally twice daily&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 48 hours after the 1st dose,</td>
<td>Age &gt;4 Weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and</td>
<td>• NVP 200 mg/m&lt;sup&gt;2&lt;/sup&gt; of BSA/dose orally twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. 96 hours after the 2nd dose</td>
<td>Birth to Age 1 Week:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birth Weight 1.5 to 2 kg:</td>
<td>• NVP 4 mg/kg/dose orally twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NVP 8 mg per dose orally.</td>
<td>Age 1 to 4 Weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: No calculation is required for this dose; <strong>this is the actual dose, not a mg/kg dose</strong>.</td>
<td>• NVP 6 mg/kg/dose orally twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birth Weight &gt;2 kg:</td>
<td>Age &gt;4 Weeks:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NVP 12 mg per dose orally.</td>
<td>• NVP 200 mg/m&lt;sup&gt;2&lt;/sup&gt; of BSA/dose orally twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Note: No calculation is required for this dose; <strong>this is the actual dose, not a mg/kg dose</strong>.</td>
<td>Birth to Age 6 Weeks:</td>
</tr>
<tr>
<td>RAL</td>
<td>N/A</td>
<td>N/A</td>
<td>Body Weight (kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Volume (Dose) of Suspension, RAL 10 mg/mL, to be Administered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Birth to 1 Week: Once Daily Dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Approximately 1.5 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 to &lt;3 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 to &lt;4 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 to &lt;5 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 to 4 Weeks: Twice Daily Dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Approximately 3 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 to &lt;3 kg</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>3 to &lt;4 kg</td>
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<td></td>
<td>4 to &lt;5 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 to 6 Weeks: Twice Daily Dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Approximately 6 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 to &lt;4 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 to &lt;6 kg</td>
</tr>
</tbody>
</table>

<sup>a</sup>The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when birth NAT returns negative, while others would continue empiric HIV therapy for infants at the highest risk of HIV acquisition for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, ZDV should be continued for 6 weeks. Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.

<sup>b</sup>Investigational NVP treatment dose recommended by the Panel; FDA has not approved a dose of NVP for infants <1 month of age.

<sup>c</sup>RAL dosing is increased at 1 and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4 to 6 weeks of life. No dosing information is available for preterm or low birthweight infants.

**Key to Acronyms:** 3TC = lamivudine; ARV = antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; N/A = no recommendation; NAT = nucleic acid test; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; UGT1A1 = uridine diphosphate glucotransferase; ZDV = zidovudine
Routine Assessment of Medication Adherence
in Clinical Care

- Monitor viral load. Viral load monitoring should be done more frequently after initiating or changing medications.
- Assess quantitative self-report of missed doses. Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).
- Elicit description of medication regimen. Ask patient and/or caregiver about the name/appearance, number, frequency of medications.
- Assess barriers to medication administration. Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.
- Monitor pharmacy refills. Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.
- Conduct announced and unannounced pill counts. Approaches include asking patients to bring medications to clinic or home visits, or referral to community health nursing.

Targeted Approaches to Monitor Adherence in Special Circumstances

- Implement DOT. Include brief hospitalization if indicated.
- Measure plasma drug concentration. Can be considered for particular drugs.

Approaches to Monitor Medication Adherence in Research Settings

- Measure drug concentrations in hair. Good measure of adherence over time.
- Use electronic monitoring devices. MEMS caps, Wisepill
- Use mobile phone-based technologies. Interactive voice response, SMS text messaging, mobile apps

Table 13. Evidence-Based Approaches for Monitoring Medication Adherence

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

Targeted Approaches to Monitor Adherence in Special Circumstances

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement DOT. Include brief hospitalization if indicated.</td>
</tr>
<tr>
<td>Measure plasma drug concentration. Can be considered for particular drugs.</td>
</tr>
</tbody>
</table>

Approaches to Monitor Medication Adherence in Research Settings

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure drug concentrations in hair. Good measure of adherence over time.</td>
</tr>
<tr>
<td>Use electronic monitoring devices. MEMS caps, Wisepill</td>
</tr>
<tr>
<td>Use mobile phone-based technologies. Interactive voice response, SMS text messaging, mobile apps</td>
</tr>
</tbody>
</table>

* See Clinical and Laboratory Monitoring After Initiation of Combination Antiretroviral Therapy (or After a Change in Combination Antiretroviral Therapy) regarding the frequency of adherence assessment after initiating or changing therapy.

* See Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection regarding indications for therapeutic drug monitoring.

Sources:


Key to Acronyms: apps = applications; DOT = directly observed therapy; MEMS = Medication Event Monitoring System
Table 14. Strategies to Improve Adherence to 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 the need for treatment and adherence.</td>
</tr>
<tr>
<td>• Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or caregiver that may decrease adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.</td>
</tr>
<tr>
<td>• Identify family, friends, health team members, and others who can support adherence.</td>
</tr>
<tr>
<td>• Educate patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.</td>
</tr>
<tr>
<td>• Work with the patient and family to make specific plans for taking medications as prescribed and supporting adherence. Assist them to arrange for administration in day care, school, and other settings, when needed. Consider home delivery of medications.</td>
</tr>
<tr>
<td>• Establish readiness to take medication through practice sessions or other means.</td>
</tr>
<tr>
<td>• Schedule a home visit to review medications and determine how they will be administered in the home setting.</td>
</tr>
<tr>
<td>• In certain circumstances, consider a brief period of hospitalization at the start of therapy 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, pill size, and number of pills.</td>
</tr>
<tr>
<td>• When choosing a regimen, consider 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 AEs; provide anticipatory guidance for management of AEs.</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 and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up Intervention Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.</td>
</tr>
<tr>
<td>• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.</td>
</tr>
<tr>
<td>• Use patient education aids including pictures, calendars, and stickers.</td>
</tr>
<tr>
<td>• Encourage use of pill boxes, reminders, mobile apps, alarms, and timers.</td>
</tr>
<tr>
<td>• Provide follow-up clinic visits, telephone calls, and text messages 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, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.</td>
</tr>
<tr>
<td>• Consider DOT at home, in the clinic, or in certain circumstances, such as during a brief inpatient hospitalization.</td>
</tr>
<tr>
<td>• Consider gastrostomy tube use in certain circumstances.</td>
</tr>
<tr>
<td>• Information on other interventions to consider can be found at the Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions.</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** apps = applications; ARV = antiretroviral; AE = adverse effect; DOT = directly observed therapy
Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 3)

<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>Global CNS Depression Depression</td>
<td>LPV/r oral solution (contains both ethanol and propylene glycol as excipients)</td>
<td>Onset: • 1–6 days after starting LPV/r</td>
<td>Unknown, rare case reports</td>
<td>Prematurity</td>
<td>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.</td>
<td>Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation</td>
<td></td>
<td>Low birth weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neonates/Premature Infants: • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)</td>
<td></td>
<td>Aged &lt;14 days (whether premature or term)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric Symptoms and Other CNS Manifestations</td>
<td>EFV</td>
<td>Onset: • For many symptoms, onset is 1–2 days after starting EFV • Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% of participants experienced persistent symptoms at 12 months and in another report, half of discontinuations occurred after 12 months.</td>
<td>Variable, depending on age, symptom, and assessment method Children: • 24% for any EFV-related CNS manifestations in 1 case series, with 18% of participants requiring drug discontinuation. • 11% (5/45 participants) incidence of new-onset seizures reported in 1 study in children aged &lt;36 months, 2 of whom had alternative causes for seizures. • Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels. Adults: • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.</td>
<td>Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL Presence of CYP450 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 TT genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants) Prior history of psychiatric illness or use of psychoactive drugs</td>
<td>Administer EFV on an empty stomach, preferably at bedtime. Prescreen for and avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs. TDM can be considered in the context of a child with mild or moderate EFV-associated toxicity.</td>
<td>If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration &gt;4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation (May Include 1 or More of the Following) Neuropsychiatric Symptoms: • Abnormal dreams • Psychosis • Suicidal ideation or attempted/ completed suicide Other CNS Manifestations: • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration • Seizures (including absence seizures)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  (Last updated May 22, 2018; last reviewed May 22, 2018)  (page 2 of 3)

<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>
| Neuropsychiatric Symptoms and Other CNS Manifestations, continued | EFV, continued | • Cerebellar dysfunction (tremor, dysmetria, ataxia)  
**Note:** CNS side effects such as impaired concentration, abnormal dreams, or sleep disturbances may be more difficult to assess in children. |  
• 1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported; |  |  |  |
| | RPV | Onset:  
• Most symptoms occur in the first 4–8 weeks of treatment  
Presentation  
Neuropsychiatric Symptoms:  
• Depressive disorders  
• Suicidal ideation  
• Abnormal dreams/nightmares  
Other CNS Manifestations:  
• Headache  
• Dizziness  
• Insomnia  
• Somnolence | Adults:  
• CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (mostly Grade 1). Depressive disorders of all severity grades were reported in 9% of patients, and were severe, requiring RPV discontinuation in 1% of patients.  
Children:  
• Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including 1 suicide attempt.  
• Somnolence reported in 14% (5/36) of children. | Prior history of neuropsychiatric illness | Monitor carefully for depressive disorders and other CNS symptoms. | Consider drug substitution in cases of severe symptoms. |
| | RAL | Onset:  
• As early as 3–4 days after starting RAL  
Presentation:  
• Increased psychomotor activity  
• Headaches  
• Insomnia  
• Depression  
• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia) | Adults:  
• Headache  
• Insomnia (<5% in adult trials)  
• Rare case reports of cerebellar dysfunction in adults  
Children:  
• Increased psychomotor activity reported in 1 child. | Elevated RAL concentrations  
Co-treatment with TDF or PPI or inhibitors of UGT1A1  
Prior history of insomnia or depression | Prescreen for psychiatric symptoms.  
Monitor carefully for CNS symptoms.  
Use with caution in the presence of drugs that increase RAL concentration. | Consider drug substitution (RAL or co-administered drug) in cases of severe insomnia or other neuropsychiatric symptoms. |
### Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity

(Updated May 22, 2018; last reviewed May 22, 2018)

<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>
| **Neuropsychiatric Symptoms and Other CNS Manifestations, continued** | DTG | Onset: 7–30 days after starting DTG | **Children:**  
**Presentation**  
Neuropsychiatric Symptoms:  
- Depression or exacerbation of preexisting depression  
- Anxiety  
- Suicidal ideation or attempted/completed suicide  
**Other CNS Manifestations (Generally Mild):**  
- Insomnia  
- Dizziness  
- Headache | **Children:**  
CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.  
**Adults:**  
- Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common and usually mild. More severe symptoms that require drug discontinuation are less common, occurring in <1% patients in Phase 3 trials, but these severe symptoms are reported with increasing frequency (4% to 10%) in recent post-marketing reports. | Pre-existing depression or other psychiatric illness  
Higher frequency of neuropsychiatric symptoms reported when co-administered with ABC | Use with caution in the presence of psychiatric illness, especially depression.  
Discontinuation resulted in resolution of neuropsychiatric symptoms in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation).  
For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time. |
| **Intracranial Hemorrhage (ICH)** | TPV | Onset: 7–513 days after starting TPV | **Children:**  
- No cases of ICH reported in children.  
**Adults:**  
- In premarket approval data in adults, 0.23/100 py or 0.04–0.22/100 py in a retrospective review of 2 large patient databases. | Unknown; prior history of bleeding disorder or risk factors for bleeding reported for most patients in case series. | Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.  
Discontinue TPV if ICH is suspected or confirmed. |

**Key to Acronyms:**  
**ABC** = abacavir;  
**ARV** = antiretroviral;  
**CNS** = central nervous system;  
**CYP** = cytochrome P;  
**DTG** = dolutegravir;  
**EEG** = electroencephalogram;  
**EFV** = efavirenz;  
**ICH** = intracranial hemorrhage;  
**LPV/r** = lopinavir/ritonavir;  
**PPI** = proton pump inhibitor;  
**py** = patient years;  
**RAL** = raltegravir;  
**RPV** = rilpivirine;  
**TDF** = tenofovir disoproxil fumarate;  
**TDM** = therapeutic drug monitoring;  
**TPV** = tipranavir;  
**UGT** = uridine diphosphate-glucurononyl transferase
References


17. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted...


### Table 15b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

(List updated May 22, 2018; last reviewed May 22, 2018)

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<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><strong>Dyslipidemia</strong></td>
<td><strong>Pis:</strong> All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. <strong>NRTIs:</strong> [Especially d4T] [Lower incidence reported with TDF than TAF] <strong>NNRTIs:</strong> [Lower incidence reported with NVP, RVP, and ETR than EFV]</td>
<td><strong>Onset:</strong> As early as 2 weeks to months after beginning therapy <strong>Presentation Pis:</strong> ↑LDL-C, TC, and TG <strong>Pis:</strong> ↑LDL-C, TC, and TG <strong>TDF:</strong> ↑LDL-C, TC, and HDL-C</td>
<td>Reported frequency varies with specific ARV regimen, duration of ART, and specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% in young children receiving LPV/r. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Higher abnormal fasting serum lipids in EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF regimen in studies of treatment-naive adults. Increase in serum lipids from baseline also noted in adolescents receiving EVG/COBI/FTC/TAF.</td>
<td>Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome Fat maldistribution</td>
<td>Prevention: • Low-fat diet • Exercise • Smoking-prevention counseling • Do not use d4T Monitoring: <strong>Adolescents and Adults:</strong> • Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPS twice (&gt;2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy. <strong>Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:</strong> • Obtain nonfasting screening lipid profiles at entry into care and then, if levels are normal, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests. <strong>Children with Lipid Abnormalities and/or Additional Risk Factors:</strong> • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). <strong>Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:</strong> • Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy.</td>
<td>Assessment of additional CVD risk factors should be done in all patients. Patients living with HIV are considered to be at moderate risk of CVD. Counsel on lifestyle modification and dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars, particularly in cases of ↑TG, elimination of trans fat in the diet, increase in physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician. ART regimen changes can be considered. Discontinue d4T or substitute a PI-sparing regimen or PI-based regimen with a more favorable lipid profile. Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails. Some experts suggest treating children receiving ARV drugs according to NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL-C ≥190 mg/dL, regardless of additional risk factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions. The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL, while minimizing side effects and maintaining viral control.</td>
</tr>
</tbody>
</table>
### Table 15b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

*Last updated May 22, 2018; last reviewed May 22, 2018* (page 2 of 2)

<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    |                 |                             |                     |             | • If minimal alterations in AST, ALT, and CK, monitor every 3–4 months in the first year and every 6 months thereafter (or as clinically indicated).<sup>a</sup>  
• Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents. | Statins such as pravastatin, atorvastatin, or rosvastatin<sup>c</sup> can be considered.<sup>d</sup> Pravastatin has lower lipid-lowering potency compared to other statins.  
Statin-induced lipid lowering effect appears more pronounced than ARV substitution. Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.<sup>c</sup> Statins may also increase the risk of insulin resistance and type 2 diabetes mellitus, but data are conflicting. Risks must be weighed against potential benefits. Cholesterol absorption inhibitors (e.g., ezetimibe) can be considered as alternatives.  
Drug therapy for severe hypertriglyceridemia (TG ≥500 mg/dL) can be considered. Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used.  
The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.|<sup>d</sup>d4T is no longer recommended for use in an ARV regimen

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<sup>a</sup> Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides from nonfasting blood samples and follow up abnormal values with a test done in the fasted state.

<sup>b</sup> Refer to NHLBI guidelines at [https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_full.pdf](https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_full.pdf).

<sup>c</sup> 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.

<sup>d</sup> Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (due to being potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (except for pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosvastatin (Crestor®), fluvastatin, and ezetimibe (Zetia®) are approved for use in children aged ≥10 years. For additional information, see the PI, NNRTI, NRTI, and INSTI Drug Interactions Tables in the Adult and Adolescent Guidelines.

<sup>e</sup>d4T is no longer recommended for use in an ARV regimen

**Key to Acronyms:** ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FLP = fasting lipid profile; FTC = emtricitabine; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDT-C = low-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglyceride
References


33. Calza L, Colangeli V, Magistrelli E, et al. No correlation between statin exposure and incident diabetes mellitus in HIV-1-infected patients receiving combination


### Table 15c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects  (Last updated May 22, 2018; last reviewed May 22, 2018)  (page 1 of 2)

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<thead>
<tr>
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<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>Nausea/Vomiting</td>
<td>All ARVs, but most notably— NRTIs:</td>
<td>Onset: • Early Presentation: • Nausea, emesis—may be associated with anorexia and/or abdominal pain</td>
<td>Varies with ARV agent; 10% to 30% in some series</td>
<td>Unknown</td>
<td>Instruct patient to take PIs with food. Monitor for weight loss, ARV adherence.</td>
<td>Reassure patient that these adverse effects generally improve over time (usually 6–8 weeks). Supportive care. In extreme or persistent cases, use antiemetics or switch ARV regimen.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>PIs: • Particularly NFV, LPV/r, and DRV/r NRTIs: • ddl and d4T at a higher rate than 3TC or FTC</td>
<td>Onset: • Early Presentation: • Generally soft, more frequent stools</td>
<td>Varies with ARV agent; generally ≤15% (range 5% to 30%)</td>
<td>Unknown</td>
<td>Monitor for weight loss, dehydration.</td>
<td>If prolonged or severe, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea. Reassure patient that this adverse effect generally improves over time (usually 6–8 weeks). Consider switching ARV regimen in persistent and severe cases. Although treatment data in children are lacking, potentially useful modalities include: • Dietary modification • Bulk-forming agents (psyllium) • Antimotility agents (loperamide) • Crofelemer is FDA-approved for treatment of ART-associated diarrhea only in adults ≥18 years of age; no pediatric data available.</td>
</tr>
</tbody>
</table>

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*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*  
Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 2/21/2019
### Table 15c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects *(Last updated May 22, 2018; last reviewed May 22, 2018)* (page 2 of 2)

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<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>Pancreatitis</td>
<td>More Common:</td>
<td>Onset:</td>
<td>&lt;2% in recent series</td>
<td>Use of concomitant medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin)</td>
<td>Do not use ddI or d4T (individually or together) as part of an ARV regimen.</td>
<td>Discontinue offending agent—avoid reintroduction. Manage symptoms of acute episode. If associated with hypertriglyceridemia, consider interventions to lower TG levels.</td>
</tr>
<tr>
<td></td>
<td>ddI, d4T</td>
<td>• Anytime, usually after months of therapy</td>
<td></td>
<td>Hypertension</td>
<td>Alcohol use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(especially if administered concurrently)</td>
<td>Presentation:</td>
<td></td>
<td>Hypertriglyceridemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare:</td>
<td>• Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)</td>
<td></td>
<td>Advanced disease Previous episode of pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RTV-boosted PIs</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Other ARVs</td>
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<td></td>
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</tr>
</tbody>
</table>

* ddI, d4T, and NFV are no longer recommended; these ARVs should not be used (individually or together) as part of an ARV regimen. Co-administration of ddI and d4T is contraindicated (no exceptions).

**Key to Acronyms:** 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ ritonavir; FDA = Food and Drug Administration; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

### References


### Table 15d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects

**Last updated May 22, 2018; last reviewed May 22, 2018**

<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><strong>Anemia</strong></td>
<td>ZDV</td>
<td>Onset: Variable, weeks to months</td>
<td>Newborns Exposed to HIV: Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir.</td>
<td>Newborns Exposed to HIV: Premature birth, In utero exposure to ZDV-containing regimens, Advanced maternal HIV, Neonatal blood loss, Combination ARV prophylaxis, particularly with ZDV plus 3TC&lt;br&gt;Children with HIV Taking ARVs: Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency), Myelosuppressive drugs (e.g., TMP-SMX, rifabutin), Iron deficiency, Advanced or poorly controlled HIV disease, Malnutrition</td>
<td>Newborns Exposed to HIV: Obtain CBC at birth. Consider repeat CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or known to have low birth Hgb) and if ZDV is continued beyond 4 weeks. Children with HIV Taking ARVs: Avoid ZDV in children with severe anemia when alternative agents are available. Obtain CBC as part of routine care (see Clinical and Laboratory Monitoring).</td>
<td>Preterm infant: None required—detected if CBC obtained as part of routine care (see Clinical and Laboratory Monitoring section). Children with HIV Taking ARVs: Discontinue non-ARV, marrow-toxic drugs, if feasible. Treat coexisting iron deficiency, OIs, and malignancies. For persistent severe anemia thought to be associated with ARVs (typically macrocytic anemia), switch to a regimen that does not contain ZDV.</td>
</tr>
<tr>
<td><strong>Macrocytosis</strong></td>
<td>ZDV</td>
<td>Onset: Within days to weeks of starting therapy, MCV often &gt;100 fL</td>
<td>&gt;90% to 95%, all ages</td>
<td>None</td>
<td>None required—detected if CBC obtained as part of routine care (see Clinical and Laboratory Monitoring section).</td>
<td>None required</td>
</tr>
</tbody>
</table>
Table 15d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects  
(Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

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<tr>
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<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Neutropenia<sup>a</sup> | ZDV | Onset:  
• Variable  
Presentation:  
• Asymptomatic | Newborns Exposed to HIV:  
• Rare  
Children with HIV Taking ARVs:  
• 2% to 4% of children on ARVs  
• Highest rates with ZDV-containing regimens | Newborns Exposed to HIV:  
• In utero exposure to ARVs  
Combination ARV prophylaxis, particularly with ZDV plus 3TC  
Children with HIV Taking ARVs:  
• Advanced or poorly controlled HIV infection  
• Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin) | Children with HIV Taking ARVs:  
• Obtain CBC as part of routine care. | Newborns Exposed to HIV:  
• No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC reaches <500 cells/mm<sup>3</sup>.  
ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV).  
Children with HIV Taking ARVs:  
• Discontinue non-ARV marrow-toxic drugs, if feasible.  
• Treat coexisting OIs and malignancies.  
• For persistent severe neutropenia thought to be associated with ARVs, change to a regimen that does not contain ZDV. |

<sup>a</sup> HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

**Key to Acronyms:** 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; dL = deciliter; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

**References**


### Table 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

*Last updated May 22, 2018; last reviewed May 22, 2018* (page 1 of 2)

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<tr>
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<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Hepatitis       | Most ARVs have been associated with hepatitis, but there is a strong association with NVP, EFV, and TPV. NVP, EFV, ABC, RAL, and MVC have been associated with hepatitis in context of HSRs. NRTIs have been associated with lactic acidosis and hepatic steatosis, especially ZDV, d4T, and ddI (co-administering d4T and ddI poses the highest risk). d4T or ddI are no longer recommended for use in an ARV regimen. | Onset:  
• An acute toxic hepatitis most commonly occurs within the first few months of therapy (but can occur later).  
• Steatosis presents after months to years of therapy.  
• Patients with HBV coinfected may develop flare of hepatitis with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if receiving only 1 anti-HBV agent). Note that HBV has a high genetic barrier for resistance to TDF and TAF.  
• Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-coinfection. | Uncommon | HBV or HCV coinfection  
Underlying liver disease  
Use of other hepatotoxic medications and supplements (e.g., St. John’s wort [*Hypericum perforatum*], chaparral [*Larrea tridentata*], germander [*Teucrium chamaedrys*])  
Alcohol use  
Pregnancy  
Obesity  
*For NVP-Associated Hepatic Events in Adults:*  
• Female with pre-NVP CD4 count >250 cells/mm²  
• Male with pre-NVP CD4 count >400 cells/mm²  
• Population-specific HLA types*  
• Higher drug concentrations for PIs, particularly TPV | Prevention:  
• Avoid concomitant use of hepatotoxic medications.  
• Do not use d4T or ddI (individually or together); co-administration is contraindicated (no exceptions).  
• In patients with elevated hepatic enzymes (>5 to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP.  
**Monitoring**  
For ARVs Other Than NVP:  
• Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT).  
For NVP:  
• Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months. | Evaluate for other infectious and non-infectious causes and monitor closely.  
**Asymptomatic:**  
• Potentially offending ARVs should be discontinued if ALT or AST is >5 times ULN.  
**Symptomatic:**  
• Discontinue all ARVs and other potentially hepatotoxic drugs.  
• If a patient experiences hepatitis attributed to NVP, it should be permanently discontinued.  
• Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV. |
### Table 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

**Last updated May 22, 2018; last reviewed May 22, 2018**

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<th>Management</th>
</tr>
</thead>
</table>
| **Indirect Hyperbilirubinemia** | ATV (with either RTV or COBI), IDV | Onset: 
  • First months of therapy  
  Presentation:  
  • May be asymptomatic or associated with jaundice  
  • Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.  
  • Normal AST and ALT | In long-term follow-up, 9% of children receiving ATV had at least 1 total bilirubin level >5 times ULN and 1.4% experienced jaundice. | N/A | Prevention:  
  • IDV is not FDA-approved or recommended for use in the pediatric population. | Isolated indirect hyperbilirubinemia is not indication for cessation of a potentially offending ARV. Psychological impact of jaundice should be evaluated, and alternative agents considered. |

| **Non-Cirrhotic Portal Hypertension** | d4T, ddI | 
  d4T or ddI are no longer recommended for use in an ARV regimen. | Onset: 
  • Generally after years of therapy  
  Presentation:  
  • GI bleeding, esophageal varices, hypersplenism  
  • Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (due to hypersplenism) | Rare | Prevention:  
  • Do not use d4T, or ddI (individually or together); co-administration is contraindicated (no exceptions). | Discontinue potentially offending agents. Manage complications of GI bleeding and esophageal varices. |

#### Notes:

* For example, HLA-DRB1*0101 in whites, HLA-DRB1*0102 in South Africans, and HLA-B35 in Thai and whites.

* Less frequent monitoring can be considered in children whose clinical status is stable for more than 2–3 years (see **Clinical and Laboratory Monitoring of Pediatric HIV Infection**).

**Key to Acronyms:**

- 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; COBI = cobicistat; d4T = stavudine; ddI = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; FDA = Food and Drug Administration; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine
## References

### General Reviews


### Hepatic Events and NRTIs


### Hepatic Events and NNRTIs


### Hepatic Events and NRTIs plus NNRTIs


### Hepatic Events and PIs including Indirect Hyperbilirubinemia


13. Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naive and


**HIV and Hepatitis B/C Coinfections**


**Nodular Regenerative Hyperplasia and Noncirrhotic Portal Hypertension**


### Table 15f. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus

*Last updated May 22, 2018; last reviewed May 22, 2018*

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors for Type 2 DM</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Resistance, Asymptomatic Hyperglycemia, DM,a</td>
<td>NRTIs:</td>
<td>Onset: Week to months after beginning therapy</td>
<td>Children:</td>
<td>Risk Factors for Type 2 DM</td>
<td>Prevention:</td>
<td>Counsel on lifestyle modification (e.g., a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increased physical activity; cessation of smoking); recommend consultation with dietitian. Change NRTI backbone (e.g., from ZDV, d4T, or ddI to TAF, TDF, or ABC). For Either RPG ≥200 mg/dL or Symptoms of DM or FPG ≥126 mg/dL: Impaired fasting glucose, 0% to 7%</td>
</tr>
<tr>
<td></td>
<td>• ZDV</td>
<td></td>
<td>• High BMI (obesity)</td>
<td>• Lipodystrophy</td>
<td>• Do not use d4T or ddI (individually or together). Co-administration is contraindicated (no exceptions). Avoid ZDV when possible. Monitoring: Monitor for signs of DM, change in body habitus, and acanthosis nigricans.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• d4T</td>
<td></td>
<td></td>
<td>• Metabolic syndrome</td>
<td>Obtain RPG Levels at:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ddI</td>
<td></td>
<td></td>
<td>• Family history of DM</td>
<td>• Initiation of ARV therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>d4T or ddI are no longer recommended for use in an ARV regimen.</td>
<td></td>
<td></td>
<td>• Lipodystrophy</td>
<td>• 3–6 months after therapy initiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIs:</td>
<td>Presentation: Symptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay</td>
<td></td>
<td>• High BMI (obesity)</td>
<td>• Once a year thereafter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• LPV/r</td>
<td>• Symptomatic DM (rare)</td>
<td></td>
<td></td>
<td>For RPG ≥140 mg/dL:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rarely other PIs</td>
<td></td>
<td></td>
<td></td>
<td>• Obtain FPG performed after 8-hour fast and consider referral to endocrinologist.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For Either RPG ≥140 mg/dL plus Symptoms of DM or FPG ≥126 mg/dL:</td>
<td></td>
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<tr>
<td></td>
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<td></td>
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<td></td>
<td>Patient meets diagnostic criteria for DM; consult endocrinologist.</td>
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<td></td>
<td>FPG 100–125 mg/dL:</td>
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<td></td>
<td>• Impaired FPG is suggestive of insulin resistance; consult endocrinologist.</td>
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<td></td>
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<td>FPG &lt;100 mg/dL:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Normal FPG, but Does Not Exclude Insulin Resistance:</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recheck FPG in 6–12 months.</td>
<td></td>
</tr>
</tbody>
</table>

---

3 Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity. Insulin resistance is often defined as elevated insulin levels for the level of glucose observed; impaired FPG as an FPG of 100–125 mg/dL; impaired glucose tolerance as an elevated 2-hour PG of 140–199 mg/dL in a 75 g-OGTT (or if <43 kg, 1.75 g/kg of glucose up to a maximum of 75 g); and diabetes mellitus as either an FPG ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an 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, HgbA1c, or glucose tolerance without consultation with an endocrinologist. These guidelines are instead based on the readily available RPG and FPG levels.

---

**Key to Acronyms:** ABC = abacavir; ARV = antiretroviral; BMI = body mass index; d4T = stavudine; ddI = didanosine; dL = deciliter; DM = diabetes mellitus; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine
References


### Table 15g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

**(Last updated May 22, 2018; last reviewed May 22, 2018)**

<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><strong>Lactic Acidosis</strong></td>
<td>NRTIs: d4T and ddI are not recommended in an ARV regimen. 3TC, FTC, ABC, TAF, and TDF are less likely to induce mitochondrial dysfunction of clinical significance.</td>
<td>Onset: 1–20 months after starting therapy (median onset was 4 months in 1 case series) Presentation Usually Insidious Onset of a Combination of Signs and Symptoms: Generalized fatigue, weakness, and myalgias Vague abdominal pain, weight loss, unexplained nausea, or vomiting Dyspnea Peripheral neuropathy</td>
<td>The following information is based on studies that included d4T and ddI. Chronic, Asymptomatic Hyperlactatemia (2.1–5.0 mmol/L) Adults: 15% to 35% of adults receiving NRTI therapy for &gt;6 months Children: 29% to 32% Symptomatic Severe Hyperlactatemia (&gt;5.0 mmol/L) Adults: 0.2% to 5.7%</td>
<td>Adults: Female sex High BMI Chronic HCV infection African-American race Prolonged NRTI use (particularly d4T and ddI) Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline) Co-administration of TDF with metformin Overdose of propylene glycol CD4 count &lt;350 cells/mm³ Acquired riboflavin or thiamine deficiency Possibly pregnancy</td>
<td>As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.</td>
<td>Lactate 2.1–5.0 mmol/L (Confirmed with Second Test): Replace ddI and d4T with other ARVs. Lactate &gt;5.0 mmol/L (Confirmed with Second Test) or &gt;10.0 mmol/L (Any 1 Test): Discontinue all ARVs. Provide supportive therapy (IV 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, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) Following resolution of clinical and laboratory abnormalities, resume therapy, either with a NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to induce mitochondrial dysfunction (ABC, TAF, or TDF preferred; possibly FTC or 3TC), and lactate should be monitored monthly for at least 3 months.</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>

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

* Management can be initiated before the results of the confirmatory test.

*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* 43

Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 2/21/2019
Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; ZDV = zidovudine

References

General Reviews


Fatal Lactic Acidosis


Risk Factors


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 2/21/2019


Monitoring and Management


### Table 15h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy  
*(Last updated May 22, 2018; last reviewed May 22, 2018)*

<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 (Fat Maldistribution) | See below for specific associations. | Onset:  
• Trunk and limb fat initially increase; peripheral fat wasting may not appear for 12–24 months after ART initiation. | Varies greatly depending upon measure and comparator group. Frequency may be up to 15% with current regimens. | Genetic predisposition  
Puberty  
HIV-associated inflammation  
Older age  
Longer duration of ART  
Body habitus | See below. | See below.  
Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs.  
Improvement following regimen change is variable. Improvement may occur after several months or years, or it may not occur at all. |

**Central Lipohypertrophy** or **Lipo-accumulation**  
Can occur in the absence of ART, but most often associated with PIs and EFV.  
**Presentation:**  
• Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females, particularly with EFV.  
**Prevention:**  
• Calorically appropriate low-fat diet and exercise  
**Monitoring:**  
• BMI measurement  
• Body circumference and waist-hip ratio  
**Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate healthy diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training).**  
**Recommend smoking cessation (if applicable) to decrease future CVD risk.**  
**Consider switching patient from PIs and EFV to an INSTI.**  
**Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:**  
• Recombinant human growth hormone  
• Growth hormone-releasing hormone  
• Metformin  
• Thiazolidinediones  
• Recombinant human leptin  
• Anabolic steroids  
• Liposuction
### General Reviews


### References

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

### Table 15h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated May 22, 2018; last reviewed May 22, 2018)

<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>Facial/Peripheral Lipoatrophy</td>
<td>Most associated with thymidine analogue NRTIs (d4T &gt; ZDV)</td>
<td>Presentation: • Thinning of subcutaneous fat in face, buttocks, and extremities, measured as a decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.</td>
<td>• Up to 15% with currently used regimens</td>
<td>Underweight before ART</td>
<td>Prevention: • Do not use ddl or d4T (individually or together); they are no longer recommended as part of an ARV regimen. Co-administration of ddl and d4T is contraindicated (no exceptions). Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.</td>
<td>Replace ZDV with other NRTIs if possible. d4T should never be used. Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children: • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat transplantation • Thiazolidinediones</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; CVD = cardiovascular disease; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine


**Associated ARVs/Etiology**


**Management**


32. Innes S, Harvey J, Collins I, Cotton M, Judd A. Lipoatrophy/lipohypertrophy outcomes after ART switch in children in UK/Ireland. 22nd Conference on Retroviruses and Opportunistic Infections; 2016; Boston, MA.


<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><strong>Urolithiasis/Nephrolithiasis</strong></td>
<td>ATV, IDV</td>
<td>Onset: • Weeks to months after starting therapy</td>
<td>ATV-related nephrolithiasis occurs in &lt;10% of patients.</td>
<td>In adults, elevated urine pH (&gt;5.7)</td>
<td>Prevention: • Maintain adequate hydration. • IDV is not FDA-approved for use in children and should be avoided.</td>
<td>Provide adequate hydration and pain control; consider using alternative ARV. If patient is on IDV, discontinue.</td>
</tr>
<tr>
<td></td>
<td>DRV causes crystalluria, but it is not associated with nephrolithiasis.</td>
<td>Clinical Findings: • Crystalluria • Hematuria • Pyuria • Flank pain • Sometimes increased creatinine</td>
<td>IDV-related nephrolithiasis occurs more often in children (29%) than adults (12.4%).</td>
<td>Unknown in children</td>
<td>Monitoring: • Obtain urinalysis at least every 6–12 months.</td>
<td></td>
</tr>
<tr>
<td><strong>Renal Dysfunction</strong></td>
<td>TDF</td>
<td>Onset: • Variable; in adults, weeks to months after initiation of therapy</td>
<td>Adults: • Approximately 2% with increased serum creatinine • Approximately 0.5% with severe renal complications</td>
<td>Risk May Increase in Children with the Following Characteristics: • Aged &gt;6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • Hypertension • Diabetes</td>
<td>Monitor urine protein, glucose or urinalysis, and serum creatinine at 3- to 6-month intervals. For patients taking TDF, some panelists add serum phosphate to the list of routine labs to monitor.</td>
<td>If TDF is the likely cause, consider using alternative ARV. TAF has significantly less toxicity than TDF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypophosphatemia appears at a median of 18 months. • Glucosuria may occur after a year of therapy. • Abnormal urine protein/osmolality ratio may be an early indicator.</td>
<td>Children: • Approximately 4% with hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy, advanced HIV infection, or concomitant use of ddI.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Presentation More Common: • Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Less Common: • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria</td>
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</tbody>
</table>

*ddI is no longer recommended and should be discontinued.*
### Table 15i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

(Last updated May 22, 2018; last reviewed May 22, 2018)  (page 2 of 2)

<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>Elevation in Serum Creatinine</td>
<td>DTG, COBI, RPV</td>
<td>Onset: • Within a month of starting treatment</td>
<td>Common</td>
<td>N/A</td>
<td>Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by &gt;0.4 mg/dL or if increases continue over time.</td>
<td>No need to change therapy. Reassure patient about the benign nature of the laboratory abnormality.</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; IDV = indinavir; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

### References


### Table 15j. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis *(Last updated May 22, 2018; last reviewed May 22, 2018)*

<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>Osteopenia and Osteoporosis</td>
<td>Any ART regimen</td>
<td>Onset: Any age; decrease in BMD usually seen soon after initiation of ART.</td>
<td>BMD z Score Less Than -2.0</td>
<td>Longer duration and greater severity of HIV disease</td>
<td>Prevention: • Ensure sufficient calcium intake and vitamin D sufficiency. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone). • Use TAF instead of TDF whenever possible. Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories).</td>
<td>Same options as for prevention. Consider changing the ARV regimen (e.g., switching from TDF to TAF, and/or from LPV/r to EFV or an INSTI whenever possible). Treat with vitamin D3 to raise serum 25-OH-vitamin D concentrations to &gt;30 ng/mL. The role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.</td>
</tr>
<tr>
<td></td>
<td>Specific Agents</td>
<td>Presentation: Usually asymptomatic. Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma).</td>
<td>&lt;10% in U.S. cohorts</td>
<td>Vitamin D insufficiency/deficiency Delayed growth or pubertal delay Low BMI Lipodystrophy Non-black race Smoking Prolonged systemic corticosteroid use Medroxyprogesterone use Lack of weight-bearing exercise</td>
<td>Monitoring: • Obtain a DXA.</td>
<td></td>
</tr>
<tr>
<td>of Concern:</td>
<td>TDF</td>
<td></td>
<td>Approximately 20% to 30% in international cohorts</td>
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<tr>
<td></td>
<td>PIs, especially</td>
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<td>**</td>
</tr>
<tr>
<td>LPV/r</td>
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</tbody>
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Some experts periodically measure 25-OH-vitamin D. This is especially important in youth with HIV infection who live in urban areas; the prevalence of vitamin D insufficiency is high in that population.

Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts obtain a DXA at baseline and every 6 to 12 months for prepubertal children and for children in early puberty who are initiating treatment with TDF. Obtaining a DXA could also be considered for adolescent women on TDF and medroxyprogesterone and for children with indications not uniquely related to HIV infection (such as cerebral palsy).

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

### References

**Osteopenia and Osteoporosis**


Table 15k. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated May 22, 2018; last reviewed May 22, 2018)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Risk Factors</th>
<th>Prevention/ Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV Toxic Neuropathy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>d4T, ddI</td>
<td>Onset: • Weeks to months</td>
<td>Children: • Around 1% overall • 10% to 25% in children taking d4T</td>
<td>• Pre-existing neuropathy • Elevated triglyceride levels • Poor nutrition • More advanced HIV disease • Concomitant use of other neurotoxic agents (e.g., INH) • Some mitochondrial DNA haplogroups may have increased risk.</td>
<td>Do not use d4T, ddI, or IDV. Co-administration of ddI and d4T is contraindicated (no exceptions).</td>
<td>Investigate potential causes, including non-ARV medications and nutritional deficiencies.</td>
</tr>
<tr>
<td></td>
<td>d4T or ddI are no longer recommended for use in an ARV regimen.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discontinue offending agent.</td>
</tr>
<tr>
<td></td>
<td>Pls rarely, primarily IDV</td>
<td>Presentation: • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia • Allodynia • Decreased or absent ankle reflexes</td>
<td>Adults: • Up to 50% in adults taking d4T</td>
<td></td>
<td>Monitor for symptoms and signs of peripheral neuropathy.</td>
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<tr>
<td></td>
<td></td>
<td>Distribution: • Bilateral soles of feet, ascending to legs and fingertips</td>
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<td></td>
<td>Consider referral to a neurologist.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

<sup>b</sup> HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

Key to Acronyms: ARV = antiretroviral; d4T = stavudine; ddI = didanosine; IDV = indinavir; INH = isoniazid; PI = protease inhibitor; the Panel = The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV

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>
| Rash           | Any ARV can cause rash | Onset:  
- First few days to weeks after starting new ARV(s)  
Presentation:  
- Most rashes are mild-to-moderate, diffuse maculopapular eruptions  
Note: A rash can be the initial manifestation of systemic hypersensitivity (see SJS/TEN/EM Major and HSR sections below). | Common (>10%. Adults and/or Children):  
- NVP  
- EFV  
- ETR  
- FPV  
- FTC  
Less Common (5% to 10%):  
- ABC  
- DRV  
- TPV  
- TDF  
Unusual (2% to 4%):  
- LPV/r  
- RAL  
- MVC  
- RPV  | • Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV)  
• Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP | When Starting NVP or Restarting After Interruptions >14 Days:  
- Utilize once-daily lead-in dosing (see NVP section).  
- Avoid the use of systemic corticosteroids during NVP dose escalation.  
- Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction. | Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:  
- Most rashes will resolve without intervention; ARVs can be continued while monitoring.  
- Antihistamines may provide some relief.  
Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgia, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., conjunctivitis):  
- Manage as SJS/TEN/EM major (see below)  
Rash in Patients Receiving NVP:  
- Given elevated risk of HSR, measure hepatic transaminases.  
- If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP below).  
- Routinely assess patient for local reactions.  
- Rotate injection sites.  
- Massage area after injection.  
- Continue the agent as tolerated by the patient.  
- Ensure patient is injecting as per instructions.  
- Rotate injection sites. |

T-20  
Onset:  
- First few days to weeks after starting new ARV(s)  
Presentation:  
- Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis  
- Often multiple reactions at the same time  
Children and Adults:  
- >90% | Unknown |
## Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions

(Last updated May 22, 2018; last reviewed May 22, 2018)  
(page 2 of 5)

<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>
| SJS/TEN/EM Major | Many ARVs, especially NNRTIs (see Estimated Frequency column) | Onset:  
• First few days to weeks after starting new ARV(s)  
Presentation:  
• Initial rash may be mild, but often becomes painful, evolving to blister/ bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. Systemic symptoms may also include fever, tachycardia, malaise, myalgia, and arthralgia. | Infrequent:  
• NVP (0.3%)  
• EFV (0.1%)  
• ETR (<0.1%)  
Case Reports:  
• FPV  
• ABC  
• DRV  
• ZDV  
• ddI  
• IDV  
• LPV/r  
• ATV  
• RAL | Adults:  
• Female gender  
• Race/ethnicity (black, Asian, Hispanic) | When Starting NVP or Restarting After Interruptions >14 Days:  
• Utilize once-daily lead-in dosing (see NVP section).  
• Counsel families to report symptoms as soon as they appear. | • Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX).  
• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.  
• Corticosteroids and/or IVIG are sometimes used, but use of each is controversial.  
• Do not reintroduce the offending medication.  
• In case of SJS/TEN/EM major occurring with 1 NNRTI, many experts would avoid use of other NNRTIs. |
| DRESS | EFV, ETR, NVP, RAL, RPV, DRV | Onset:  
• 1–8 weeks after starting new ARV(s)  
Presentation:  
• Fever  
• Lymphadenopathy  
• Facial swelling  
• Morbilliform to polymorphous rash  
• Peripheral eosinophilia  
• Atypical circulating lymphocytes  
• Internal organ involvement (particularly liver and/or renal) | Rare | Unknown | When Starting NVP or Restarting After Interruptions >14 Days:  
• Utilize once-daily lead-in dosing (see NVP section).  
• Counsel families to report symptoms as soon as they appear. | • Obtain CBC, AST, ALT, and creatinine from a patient presenting with suggestive symptoms. | • Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX).  
• Role for steroids unclear; suggest consultation with specialist.  
• Provide supportive care for end-organ disease.  
• Do not reintroduce the offending medication. |
### Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions

_Last updated May 22, 2018; last reviewed May 22, 2018_ (page 3 of 5)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
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<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR</td>
<td>ABC</td>
<td>Onset</td>
<td>With First Use:</td>
<td>• Within first 6 weeks</td>
<td>• Within hours</td>
<td>• Onset: Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms (e.g., dyspnea).</td>
</tr>
</tbody>
</table>

**Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions**

_Last updated May 22, 2018; last reviewed May 22, 2018_ (page 3 of 5)
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<thead>
<tr>
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<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR</td>
<td>NVP</td>
<td>Onset:</td>
<td>4% (2.5% to 11%)</td>
<td>Adults:</td>
<td>When Starting NVP or Restarting After Interruptions &gt;14 Days:</td>
<td>• Discontinue ARVs.</td>
</tr>
</tbody>
</table>
|                 |                 | • Most frequent in the first few weeks of therapy, but can occur through 18 weeks |         | • Treatment-naive with higher CD4 count (>250 cells/mm³ in women; >400 cells/mm³ in men). | • A 2-week lead-in period with once-daily dosing, followed by dose escalation to twice daily as recommended, may reduce the risk of reaction.
|                 |                 | Presentation:                 |         | • Female sex (risk is 3-fold higher in females compared with males). | • Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions. |
|                 |                 | • Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy |         | Children:     | • Obtain AST and ALT in patients with rash. Obtain AST and ALT at baseline, before dose escalation, 2 weeks post-dose escalation, and thereafter at 3-month intervals. | • Do not re-introduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment. |
|                 |                 | • NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants. |         | • High CD4 percentage is associated with increased risk of NVP toxicity. | • Avoid NVP use in women with CD4 counts >250 cells/mm³ and in men with CD4 counts >400 cells/mm³ unless benefits outweigh risks. |
|                 |                 | • In the PREDICT study, the risk of NVP toxicity (rash, hepatotoxicity, hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages <15%. | | | • Do not use NVP as post-exposure prophylaxis outside of the neonatal period. |
| T-20, ETR       |                 | Onset:                         | Rare     | Unknown | Evaluate for hypersensitivity if the patient is symptomatic. | • Discontinue ARVs. |
|                 |                 | • Any time during therapy |         |         | • Rechallenge with T-20 or ETR is not recommended. |
The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and an expert in HIV care should be consulted. NVP should be stopped and not restarted if the rash is severe or is worsening or progressing.

Key to Acronyms:

**ABC** = abacavir; **ALT** = alanine transaminase; **ARV** = antiretroviral; **AST** = aspartate aminotransferase; **ATV** = atazanavir; **CBC** = complete blood count; **CD4** = CD4 T lymphocyte; **CYP** = cytochrome P; **ddI** = didanosine; **DRESS** = drug rash with eosinophilia and systemic symptoms; **DRV** = darunavir; **DTG** = dolutegravir; **EFV** = efavirenz; **EM** = erythema multiforme; **ETR** = etravirine; **FPV** = fosamprenavir; **FTC** = emtricitabine; **HLA** = human leukocyte antigen; **HSR** = hypersensitivity reaction; **IDV** = indinavir; **IV** = intravenous; **IVIG** = intravenous immune globulin; **LPV/r** = lopinavir/ritonavir; **MVC** = maraviroc; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NVP** = nevirapine; **PEP** = post-exposure prophylaxis; **PI** = protease inhibitor; **RAL** = raltegravir; **RPV** = rilpivirine; **SJS** = Stevens-Johnson syndrome; **T-20** = enfuvirtide; **TDF** = tenofovir disoproxil fumarate; **TEN** = toxic epidermal necrolysis; **TPV** = tipranavir; **ZDV** = zidovudine

Table 15l. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions

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<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>HSR With or without skin involvement and excluding SJS/TEN</td>
<td>MVC</td>
<td>Rash preceding hepatotoxicity</td>
<td>Rare</td>
<td>Unknown</td>
<td>• Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</td>
<td>• Discontinue all ARVs.</td>
</tr>
<tr>
<td></td>
<td>DTG</td>
<td>Rash with hepatic dysfunction</td>
<td>Rare</td>
<td>Unknown</td>
<td>• Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</td>
<td>• Discontinue all ARVs.</td>
</tr>
</tbody>
</table>

a The prescribing information for NVP states that patients experiencing rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase risk of NVP resistance because of sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and an expert in HIV care should be consulted. NVP should be stopped and not restarted if the rash is severe or is worsening or progressing.

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References


### Table 16. Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimen (page 1 of 2)

**Note:** This list is not exhaustive and does not necessarily contain all potential treatment options. Instead, it shows examples of what kinds of changes can be made. The comments provided in the table are relevant only to the potential ARV change are listed and do not include all relevant information. Please refer to the individual drug sections in [Appendix A: Pediatric Antiretroviral Drug Information](https://aidsinfo.nih.gov/guidelines) for further information.

<table>
<thead>
<tr>
<th>Current ARV Drug(s)</th>
<th>Age, Weight, and SMR Requirements</th>
<th>Potential ARV Switch</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC or 3TC Twice Daily</td>
<td>Aged ≥1 year</td>
<td>ABC once daily</td>
<td>See Abacavir and Lamivudine sections in <a href="https://aidsinfo.nih.gov/guidelines">Appendix A: Pediatric Antiretroviral Drug Information</a> for full discussion of once-daily dosing.</td>
</tr>
<tr>
<td></td>
<td>Aged ≥3 years</td>
<td>3TC once daily</td>
<td></td>
</tr>
<tr>
<td>ZDV, ddI, or d4T ²</td>
<td>Aged ≥3 months</td>
<td>ABC</td>
<td>Less long-term mitochondrial toxicity. Children aged ≥1 year can take ABC once daily (see Abacavir in <a href="https://aidsinfo.nih.gov/guidelines">Appendix A: Pediatric Antiretroviral Drug Information</a>).</td>
</tr>
<tr>
<td></td>
<td>Aged ≥2 years</td>
<td>TDF</td>
<td>TDF is a reasonable, once-daily option for HLA-B*5701–positive children who are unable to take ABC. TDF is available in low-strength combination tablets with FTC for use in children weighing ≥17 kg. TAF is preferred for children weighing ≥25 kg.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥25 kg</td>
<td>TAF ²</td>
<td>Less long-term mitochondrial toxicity. Once-daily dosing. Co-formulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone and renal toxicity. See TAF in <a href="https://aidsinfo.nih.gov/guidelines">Appendix A: Pediatric Antiretroviral Drug Information</a> for full discussion.</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>N/A</td>
<td>RAL ³</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Aged ≥3 months</td>
<td>ATV/r</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥5 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aged ≥3 years</td>
<td>DRV/r</td>
<td>DRV/r may be administered once daily in children aged ≥12 years who do not have DRV resistance mutations.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥10 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighing ≥25 kg</td>
<td>EVG as Genvoya</td>
<td>EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya). Genvoya is a complete ARV regimen.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥30 kg</td>
<td>DTG</td>
<td>Smaller pill, higher barrier to resistance given concern for adherence challenges developing in adolescents.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥12 years</td>
<td>RPV</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥35 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r Twice Daily</td>
<td>N/A</td>
<td>RAL ³</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥10 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aged ≥3 months</td>
<td>ATV/r</td>
<td>Once-daily dosing.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥5 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aged ≥3 years</td>
<td>DRV/r</td>
<td>DRV/r is administered twice daily to patients aged &lt;12 years, but may be administered once daily only in children aged ≥12 years who do not have DRV resistance mutations.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥10 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighing ≥25 kg</td>
<td>EVG as Genvoya</td>
<td>EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya). Genvoya is a complete ARV regimen.</td>
</tr>
</tbody>
</table>
Table 16. Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimen (page 2 of 2)

<table>
<thead>
<tr>
<th>Current ARV Drug(s)</th>
<th>Age, Weight, and SMR Requirements</th>
<th>Potential ARV Switch</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LPV/r Twice Daily, continued</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weighing ≥30 kg</td>
<td>DTG</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Aged ≥12 years Weighing ≥35 kg</td>
<td>RPV</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>BIC as Biktarvy</strong></td>
<td></td>
<td>Once-daily dosing. BIC is available as a component of the FDC BIC/FTC/TAF (Biktarvy). Biktarvy is a complete ARV regimen; pediatric use is investigational.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Any Multi-Pill and/or Twice-Daily Regimen</strong></td>
<td>Weighing ≥25 kg</td>
<td>EVG/CObI/FTC/TAF (Genvoya)</td>
<td>Once-daily dosing. Single pill. Alignment with adult regimens.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥30 kg</td>
<td>FTC/TAF (Descovy) plus DTG</td>
<td>Once-daily dosing. May be more desirable because of small pill sizes, even though it increases pill burden to 2 pills instead of 1.</td>
</tr>
<tr>
<td></td>
<td>Weighing ≥35 kg</td>
<td>EVG/CObI/FTC/TDF (Stribild)</td>
<td>Once-daily dosing. Single pill. Alignment with adult regimens.</td>
</tr>
<tr>
<td></td>
<td><strong>SMR 4 or 5 Aged ≥12 years Weighing ≥35 kg</strong></td>
<td>FTC/RPV/TAF (Odefsey)</td>
<td>Once-daily dosing. Single pill. Alignment with adult regimens.</td>
</tr>
<tr>
<td></td>
<td><strong>Aged ≥12 years Weighing ≥35 kg</strong></td>
<td>BIC/FTC/TAF* (Biktarvy)</td>
<td>Once-daily dosing. Single pill. Pediatric use is investigational.</td>
</tr>
<tr>
<td></td>
<td><strong>Aged ≥12 years Weighing ≥35 kg</strong></td>
<td>FTC/RPV/TDF (Complera)</td>
<td>Once-daily dosing. Single pill. Alignment with adult regimens.</td>
</tr>
<tr>
<td></td>
<td><strong>SMR 4 or 5 Weighing ≥40 kg</strong></td>
<td>ABC/DTG/3TC (Triumeq)</td>
<td>Once-daily dosing. Single pill. Alignment with adult regimens. Large pill size may be a deterrent.</td>
</tr>
</tbody>
</table>

* For infants and young children being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In clinically stable patients with undetectable viral loads who have had stable CD4 T lymphocyte cell counts for more than 6 months (24 weeks) on twice-daily ABC, the dose can be changed from twice daily to once daily.

b d4T and ddI should be replaced with a safer drug as soon as possible because of concerns about long-term adverse events (see Stavudine and Didanosine in Appendix A: Pediatric Antiretroviral Drug Information).

c For children and adolescents weighing 25 kg to <35 kg, TAF can be used in combination with an INSTI or an NNRTI, but not a boosted PI. For children and adolescents weighing ≥35 kg, TAF can be used in combination with an INSTI, NNRTI, or a boosted PI.

d RAL HD once daily is only recommended for virologically suppressed children weighing ≥50 kg.

e Biktarvy has not been FDA-approved for use in patients aged <18 years but is being studied in children and adolescents aged ≥12 years to 18 years and weighing ≥35 kg.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BIC = bictegravir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating (previously Tanner stages); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV= tenofovir; ZDV = zidovudine
Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression

Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:

- Lab error (in CD4 or viral load result)
- Misinterpretation of normal, age-related CD4 decline (i.e., the immunologic response is not actually poor)
- Low pretreatment CD4 cell count or percentage
- Adverse effects of using ZDV or the combination of TDF and ddl
- Use of systemic corticosteroids or chemotherapeutic agents
- Conditions that can cause low CD4 values, such as HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis

Poor Immunologic and Clinical Responses Despite Virologic Suppression:

- Lab error
- Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2)
- Persistent immunodeficiency soon after initiation of ART but before ART-related reconstitution
- Primary protein-calorie malnutrition
- Untreated TB
- Malignancy

Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses

- IRIS
- Previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy)
- Malnutrition
- Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy), lungs (e.g., bronchiectasis)
- New clinical event due to non-HIV illness or condition
- New, otherwise unexplained HIV-related clinical event (treatment failure)

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; ddl = didanosine; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine
Table 18. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients with Failed Antiretroviral Therapy and Evidence of Viral Resistance

<table>
<thead>
<tr>
<th>Prior Regimen</th>
<th>New Regimen Options</th>
</tr>
</thead>
</table>
| 2 NRTIs plus NNRTI | • 2 NRTIs plus PI  
• 2 NRTIs plus INSTI |
| 2 NRTIs plus PI | • 2 NRTIs plus INSTI  
• 2 NRTIs plus a different RTV-boosted PI  
• INSTI plus different RTV-boosted PI plus or minus an NNRTI and plus or minus NRTI(s) |
| 2 NRTIs plus INSTI | • 2 NRTIs plus RTV-boosted PI  
• DTG (if not used in the prior regimen) plus RTV-boosted PI plus or minus 1 or 2 NRTIs |
| Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s) | • INSTI plus 2 NRTIs (if NRTIs are fully active)  
• INSTI plus 2 NRTIs plus or minus RTV-boosted PI (if NRTIs are not fully active)  
• INSTI plus or minus RTV-boosted PI plus or minus (ETR or RPV) plus or minus NRTI(s) (if minimal NRTI activity). Consider adding T-20 and/or MVC if additional active drug[s] needed. |

* ART regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting NRTI components of an NNRTI-based regimen, where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. Regimens should contain at least two, but preferably three, fully active drugs for durable and potent virologic suppression. Please see individual drug profiles for information about age limitations (e.g., do not use DRV in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance. Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multiclass drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

**Key to Acronyms:** DTG = dolutegravir; ETR = etravirine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide
### Appendix A: Pediatric Antiretroviral Drug Information

#### Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

<table>
<thead>
<tr>
<th>Brand Name by Class</th>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>INSTIs</th>
<th>PIs</th>
<th>PK Enhancers</th>
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<tbody>
<tr>
<td></td>
<td>ABC</td>
<td>3TC</td>
<td>ZDV</td>
<td>FTC</td>
<td>TDF</td>
</tr>
<tr>
<td>NRTI</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimduo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combivir, Generic</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descovy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Epzicom, Generic</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TemixyS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trizivir, Generic</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Truvada</td>
<td></td>
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<tr>
<td>NRTI/NNRTI</td>
<td></td>
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<tr>
<td>Atripla</td>
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<tr>
<td>Complera</td>
<td></td>
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<tr>
<td>Odefsey</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symfi or Symfi Lo</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>NRTI/INSTI</td>
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<tr>
<td>Biktarvy</td>
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<tr>
<td>Triumeq</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>NNRTI/INSTI</td>
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<td>Juluca</td>
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<tr>
<td>NRTI/INSTI/COBI</td>
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<tr>
<td>Genvoya</td>
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<tr>
<td>Stribild</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NRTI/PI/COBI</td>
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<tr>
<td>Symtuza</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PI/COBI</td>
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<tr>
<td>Evotaz</td>
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<tr>
<td>Prezcobix</td>
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<tr>
<td>PI/RTV</td>
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<tr>
<td>Kaletra</td>
<td></td>
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</tr>
</tbody>
</table>

*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*

Downloaded from [https://aidsinfo.nih.gov/guidelines](https://aidsinfo.nih.gov/guidelines) on 2/21/2019
Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

This table may include recently approved FDCs that have not yet been added to individual drug sections in the Pediatric Antiretroviral Drug Information Appendix (see individual drug components for details), and it does not include FDCs for individual component drugs that were recently approved and have not been added to the Pediatric Antiretroviral Drug Appendix (e.g., Doravirine and the FDC Delstrigo).

TAF, BIC, and EVG are only available in FDC tablets. However, TAF 25 mg tablets (Vemlidy) are FDA-approved for treatment of HBV. In select circumstances, TAF might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

LPV is only available in fixed-dose tablets or solution.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; LPV = lopinavir; LPV/r = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine
Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (page 1 of 3)

This table may include recently approved FDCs that have not yet been added to individual drug sections in the Pediatric Antiretroviral Drug Information Appendix (see individual drug components for details), and it does not include FDCs for individual component drugs that were recently approved and have not been added to the Pediatric Antiretroviral Drug Appendix (e.g., Doravirine and the FDC Delstrigo).

General Considerations When Considering a Fixed-Dose Combination Tablet:

- ABC and TAF are favored over ZDV because of lower risk of NRTI-associated mitochondrial toxicity.
- TDF is more potent than ABC at high viral loads when used in regimens that do not contain an INSTI.
- TAF is favored over TDF because of the lower risk of TDF-associated bone and renal toxicity.
- TDF is generally not recommended for children with SMR 1–3 because of TDF-associated bone toxicity; however, for a child weighing <25 kg who can swallow pills, Truvada low-strength tablets offer a reasonable, once daily combination alternative to twice daily ZDV plus 3TC or an alternative to ABC.
- RPV has low potency at high viral loads, a low barrier to resistance, and requires a high fat meal for optimal absorption, so EFV or an INSTI are favored.
- BIC and DTG, second-generation INSTIs, have a higher barrier to resistance than EVG, a first-generation INSTI.
- INSTI FDC dosing for children and adolescents:
  - 25 kg: Genvoya
  - 30 kg: Descovy plus DTG (2 pills, but each is small); there is no agreed-upon DTG dose yet below 30 kg
  - Recent data identified a possible increased risk of NTDs among women who were receiving DTG at the time of conception. Specific recommendations about the initiation and use of DTG in adolescents and women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (See Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for the Use of Antiretroviral Drugs in Pregnancy).
  - Biktarvy has been studied in youth aged ≥6 years and weighing ≥25 kg but is not FDA approved for use in children or adolescents.
  - For images of most of the FDCs listed in this table, see the Antiretroviral Medications section of the National HIV curriculum. In addition, a resource from the United Kingdom illustrates the relative sizes of FDCs (see the “Intro ARV chart”). Although most of the drugs listed in the chart are the same as those in the United States, a few of the brand names are not the same as those listed in Appendix A, Table 2 below.
## Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (page 2 of 3)

<table>
<thead>
<tr>
<th>FDC by Class</th>
<th>FDC Components</th>
<th>Minimum Body Weight (kg) or Age</th>
<th>Pill Size (mm x mm)</th>
<th>Food Required for Optimal Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimduo</td>
<td>3TC 300 mg plus TDF 300 mg</td>
<td>35 kg</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Combivir and Generic 3TC/ZDV</td>
<td>3TC 150 mg plus ZDV 300 mg (scored tablet)</td>
<td>30 kg</td>
<td>18 x 7</td>
<td>No</td>
</tr>
<tr>
<td>Descovy</td>
<td>FTC 200 mg plus TAF 25 mg</td>
<td>25 kg: With INSTI or NNRTI 35 kg: With boosted PI</td>
<td>12.5 x 6.4</td>
<td>No</td>
</tr>
<tr>
<td>Epzicom and Generic ABC/3TC</td>
<td>ABC 600 mg plus 3TC 300 mg</td>
<td>25 kg</td>
<td>21 x 9</td>
<td>No</td>
</tr>
<tr>
<td>Temixys</td>
<td>3TC 300 mg plus TDF 300 mg</td>
<td>35 kg</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Trizivir and Generic ABC/3TC</td>
<td>ABC 300 mg plus 3TC 150 mg plus ZDV 300 mg</td>
<td>40 kg</td>
<td>21 x 10</td>
<td>No</td>
</tr>
<tr>
<td>Truvada</td>
<td>FTC 200 mg plus TDF 300 mg</td>
<td>35 kg</td>
<td>19 x 8.5</td>
<td>No</td>
</tr>
<tr>
<td>Truvada Low Strength</td>
<td>FTC 167 mg plus TDF 250 mg</td>
<td>28 kg</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>FTC 133 mg plus TDF 200 mg</td>
<td>22 kg</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>FTC 100 mg plus TDF 150 mg</td>
<td>17 kg</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td><strong>NRTI/NNRTI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atripla</td>
<td>EPV 600 mg plus FTC 200 mg plus TDF 300 mg</td>
<td>40 kg</td>
<td>N/A</td>
<td>Fasting</td>
</tr>
<tr>
<td>Complera</td>
<td>FTC 200 mg plus RPV 25 mg plus TDF 300 mg</td>
<td>35 kg and ≥12 years</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Odefsey</td>
<td>FTC 200 mg plus RPV 25 mg plus TAF 25 mg</td>
<td>35 kg and ≥12 years</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Symfi</td>
<td>EPV 600 mg plus 3TC 300 mg plus TDF 300 mg</td>
<td>40 kg</td>
<td>N/A</td>
<td>Unevaluated</td>
</tr>
<tr>
<td>Symfi Lo</td>
<td>EPV 400 mg plus 3TC 300 mg plus TDF 300 mg</td>
<td>35 kg</td>
<td>N/A</td>
<td>Unevaluated</td>
</tr>
<tr>
<td><strong>NRTI/INSTI</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Biktarvy</td>
<td>BIC 50 mg plus FTC 200 mg plus TAF 25 mg</td>
<td>Adults</td>
<td>15 x 8</td>
<td>No</td>
</tr>
<tr>
<td>Triumeq</td>
<td>ABC 600 mg plus DTG 50 mg plus 3TC 300 mg</td>
<td>40 kg</td>
<td>22 x 11</td>
<td>No</td>
</tr>
</tbody>
</table>
### Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (page 3 of 3)

<table>
<thead>
<tr>
<th>FDC by Class</th>
<th>FDC Components</th>
<th>Minimum Body Weight (kg) or Age</th>
<th>Pill Size (mm x mm)</th>
<th>Food Required for Optimal Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI/INSTI</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Juluca</td>
<td>DTG 50 mg plus RPV 25 mg</td>
<td>Adults</td>
<td>N/A</td>
<td>Yes</td>
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<td><strong>NRTI/INSTI/COBI</strong></td>
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<tr>
<td>Genvoya</td>
<td>EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg</td>
<td>25 kg</td>
<td>19 x 8.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Stribild</td>
<td>EVG 150 mg plus COBI 150 mg plus FTC 200 mg plus TDF 300 mg</td>
<td>35 kg</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>NRTI/PI/COBI</strong></td>
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<tr>
<td>Symtuza</td>
<td>DRV 800 mg plus COBI 150 mg plus FTC 200 mg plus TAF 10 mg</td>
<td>Adults</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PI/COBI</strong></td>
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<tr>
<td>Evotaz</td>
<td>ATV 300 mg plus COBI 150 mg</td>
<td>35 kg</td>
<td>N/A</td>
<td>Yes</td>
</tr>
<tr>
<td>Prezobix</td>
<td>DRV 800 mg plus COBI 150 mg</td>
<td>35 kg</td>
<td>N/A</td>
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<td><strong>PI/RTV</strong></td>
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<tr>
<td>Kaletra</td>
<td>LPV/r Oral Solution:</td>
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</tr>
<tr>
<td></td>
<td>• 80 mg/mL LPV plus 20 mg/mL RTV</td>
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<tr>
<td></td>
<td>Tablets:</td>
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</tr>
<tr>
<td></td>
<td>• LPV 200 mg plus RTV 50 mg</td>
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</tr>
<tr>
<td></td>
<td>• LPV 100 mg plus RTV 25 mg</td>
<td>Post-menstrual age of 42 weeks and a postnatal age of ≥14 days; No minimum weight</td>
<td></td>
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</tr>
</tbody>
</table>

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; mm = millimetre; N/A = information not available; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine