Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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These guidelines focus on infants, children, and adolescents in early puberty (SMR I-III) living with HIV in the United States.

Panel Members
The Panel is composed of approximately 32 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. 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 US 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.

Financial Disclosure
All members of the Panel submit a financial disclosure statement in writing annually, 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 (http://aidsinfo.nih.gov).

Users of the Guidelines
Providers of care to infants, children, and adolescents living with HIV in the United States

Developer
Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of OARAC

Funding Source
Office of AIDS Research, NIH and HRSA

Evidence Collection
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. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.

Recommendation Grading
Described in Table 2.

Method of Synthesizing Data
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.

Other Guidelines
These guidelines focus on infants, children, and adolescents in early puberty (SMR I-III) living with HIV. Guidance for treatment for 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 and 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 (http://www.aidsinfo.nih.gov).

Update Plan
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 yearly.

Public Comments
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 contactus@aidsinfo.nih.gov.
### 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><strong>A:</strong> 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><strong>B:</strong> 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, non randomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td><strong>C:</strong> 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>
</tr>
<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>
</tr>
<tr>
<td>Chemistries</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>Urinalysis</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 See text for details on recommended laboratory tests to obtain.
2 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 in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if not already performed (see Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Send tests appropriate to the toxicities expected from each patient's ART regimen and history (see text).
3 If ART is initiated within 30 to 90 days of a pre-therapy lab result, repeat testing may not be necessary.
4 CD4 cell count can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years.
5 If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis is considered.
6 When considering starting ARV drugs with activity against hepatitis B, specifically lamivudine-, emtricitabine-, and tenofovir-containing regimens
7 Recommended only if individual previously demonstrated no immunity to hepatitis B

Key to Acronyms: ART = antiretroviral therapy, ARV = antiretroviral, CBC = complete blood count, CD4 = CD4 T lymphocyte
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/ TaqMan v 2.0</th>
<th>Versant v 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Method</strong></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><strong>Dynamic Range (copies/mL)</strong></td>
<td>40–107</td>
<td>25–107</td>
<td>20–107</td>
<td>37–11x107</td>
</tr>
<tr>
<td><strong>Specimen volume</strong></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><strong>Manufacturer</strong></td>
<td>Abbott</td>
<td>bioMerieux</td>
<td>Roche</td>
<td>Siemens</td>
</tr>
</tbody>
</table>

* Note: Smaller volumes for children can be accommodated.

Key to Acronyms: NASBA = nucleic acid sequence-based amplification; RT-PCR = reverse transcription polymerase chain reaction

Table 5: HIV Infection Stage* Based on Age-Specific CD4 Cell Count or Percentage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Age on Date of CD4 Test</th>
<th>&lt;1 Year</th>
<th>1 to &lt;6 Years</th>
<th>≥6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cells/µL</td>
<td>%</td>
<td>Cells/µL</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>≥1,500</td>
<td>≥34</td>
<td>≥1,000</td>
<td>≥30</td>
</tr>
<tr>
<td>2</td>
<td>750–1,499</td>
<td>26–33</td>
<td>500–999</td>
<td>22–29</td>
</tr>
<tr>
<td>3</td>
<td>&lt;750</td>
<td>&lt;26</td>
<td>&lt;500</td>
<td>&lt;22</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.

Table 6: HIV-Related Symptoms

<table>
<thead>
<tr>
<th>Mild HIV-Related Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with 2 or more of the conditions listed but none of the conditions listed in Moderate Symptoms category</td>
</tr>
<tr>
<td>• Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site)</td>
</tr>
<tr>
<td>• Hepatomegaly</td>
</tr>
<tr>
<td>• Splenomegaly</td>
</tr>
<tr>
<td>• Dermatitis</td>
</tr>
<tr>
<td>• Parotitis</td>
</tr>
<tr>
<td>• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate HIV-Related Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anemia (hemoglobin &lt;8 g/dL [&lt;80 g/L]), neutropenia (white blood cell count &lt;1,000/µL [&lt;1.0 × 10⁹/L]), and/or thrombocytopenia (platelet count &lt;100 × 10³/µL [&lt;100 × 10⁹/L]) persisting for ≥30 days</td>
</tr>
<tr>
<td>• Bacterial meningitis, pneumonia, or sepsis (single episode)</td>
</tr>
<tr>
<td>• Candidiasis, oropharyngeal (thrush), persisting (&gt;2 months) in children aged &gt;6 months</td>
</tr>
<tr>
<td>• Cardiomyopathy</td>
</tr>
<tr>
<td>• Cytomegalovirus infection, with onset before 1 month</td>
</tr>
<tr>
<td>• Diarrhea, recurrent or chronic</td>
</tr>
<tr>
<td>• Hepatitis</td>
</tr>
<tr>
<td>• Herpes simplex virus (HSV) stomatitis, recurrent (&gt;2 episodes within 1 year)</td>
</tr>
<tr>
<td>• HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month</td>
</tr>
<tr>
<td>• Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome</td>
</tr>
<tr>
<td>• Leiomyosarcoma</td>
</tr>
<tr>
<td>• Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex</td>
</tr>
<tr>
<td>• Nephropathy</td>
</tr>
<tr>
<td>• Nocardiosis</td>
</tr>
<tr>
<td>• Persistent fever (lasting &gt;1 month)</td>
</tr>
<tr>
<td>• Toxoplasmosis, onset before 1 month</td>
</tr>
<tr>
<td>• Varicella, disseminated (complicated chickenpox)</td>
</tr>
</tbody>
</table>
Stage-3-Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent\(^a\)
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive\(^b\)
- 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\(^c\)
- 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\(^b\)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV\(^c\)

\(^a\) Only among children aged <6 years.

\(^b\) Only among adults, adolescents, and children aged ≥6 years.

\(^c\) 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 in treatment-naive children generally contains 1 NNRTI or 1 PI boosted with ritonavir or cobicistat or 1 INSTI plus a 2-NRTI backbone. Preferred regimens are so designated based on efficacy, ease of administration and acceptable toxicity. Alternative regimens have also demonstrated efficacy, but have disadvantages compared with preferred regimens in terms of more limited experience in children or less favorable ease of administration. Regimens should be individualized based on advantages and disadvantages of each combination (see Table 8).

For children who are receiving an effective and tolerable ART regimen, that regimen can be continued as they age even if the combination they are receiving is no longer a preferred regimen.

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants, Birth to &lt;14 Days</strong></td>
<td>2 NRTIs plus NVP</td>
</tr>
<tr>
<td>Children Aged ≥14 Days to &lt;2 Years</td>
<td>2 NRTIs plus LPV/r</td>
</tr>
<tr>
<td>Children Aged ≥2 Years to &lt;3 Years</td>
<td>2 NRTIs plus LPV/r</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2 NRTIs plus ATV/r</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus twice-daily DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2 NRTIs plus ATV/r</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus DTG&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)</strong></td>
<td>2 NRTIs plus ATV/r</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus DTG&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus once-daily DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus EVG/COBI&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)</strong></td>
<td>Refer to Adult and Adolescent Guidelines</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative Regimens</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged &gt;14 Days to &lt;3 Years</td>
<td>2 NRTIs plus NVP&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children Aged ≥4 Weeks to &lt;2 Years and Weighing ≥3 kg</td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children Aged ≥3 Months to &lt;3 Years and Weighing ≥10 kg</td>
<td>2 NRTIs plus ATV/r</td>
</tr>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus LPV/r</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2 NRTIs plus twice-daily DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus LPV/r</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)</td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RPV&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, Birth to &lt;3 Months</td>
<td>ZDV plus (3TC or FTC)</td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

<table>
<thead>
<tr>
<th>Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs, continued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥3 Months to &lt;12 Years</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥2 Weeks</td>
</tr>
<tr>
<td>Children Aged ≥3 Months</td>
</tr>
<tr>
<td>Adolescents at SMR III</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years at SMR III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-NRTI Regimens for Use in Special Circumstances in Combination with Additional Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥2 Years and Adolescents, SMR I or II</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

* If treatment initiation is planned prior to 14 days of age, NVP is the Preferred agent. 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). Consultation with an expert in pediatric HIV infection should be sought. Additional considerations regarding the use of NVP in infants aged <14 days can be located in Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection. A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks post-gestational age, based on infant genotype and the better outcomes of LPV/r in children aged <3 years.

b LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and postnatal age ≥14 days.

c RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children aged 4 weeks to 2 years.

d DRV once-daily should not be used in children aged <12 years or weighing <40 kg or if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, 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 and not sexually mature (SMR I–III) where once-daily administration is possible.

e DTG is recommended only for children and adolescents weighing ≥30 kg.

f EVG is currently recommended only in fixed-dose combination tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as Preferred for children and adolescents weighing ≥35 kg. Tablets containing EVG/COBI/FTC/TDF are recommended only for children and adolescents weighing ≥35 kg, and in SMR IV or V.

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

h ERV is licensed for use in children aged ≥3 months who weigh ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years.

i RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; COBI=cobicistat; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine
Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children

<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 | Integrase Inhibitor Class Advantages:  
• Susceptibility of HIV to a new class of ARV drugs  
• Few drug-drug interactions  
• Well-tolerated | Integrase Inhibitor Class Disadvantages:  
• Limited data on pediatric dosing or safety | |
| DTG | • Once-daily administration  
• Can give with food  
• Available as a fixed-dose combination tablet containing ABC/3TC/DTG (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 | |
| EVG | • Once-daily administration  
• Available as a fixed-dose combination tablet containing EVG/COBI/FTC/TDF (Stribild) and as a fixed-dose combination tablet containing 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 with normal glomerular clearance. | |
| RAL | • Can give with food.  
• Available in tablet, chewable tablet, and powder formulations | • Potential for rare systemic allergic reaction or hepatitis | |
| NNRTIs In Alphabetical Order | NNRTI Class Advantages:  
• Long half-life  
• Less dyslipidemia and fat maldistribution than PIs  
• PI-sparing  
• Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens. | NNRTI Class Disadvantages:  
• Single mutation can confer resistance, with cross-resistance between EFV and NVP.  
• Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP)  
• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4). | |
| EFV | • Once-daily administration  
• Available as a fixed-dose combination tablet containing EFV/FTC/TDF (Atripla)  
• Potent ARV activity  
• Can give with food (but avoid high-fat meals).  
• Capsules can be opened and added to food. | • Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects)  
• Rash (generally mild)  
• No commercially available liquid.  
• Limited data on dosing for children aged <3 years.  
• No data on dosing for children aged <3 months.  
• Use with caution in adolescent females of childbearing age. | |
| NVP | • Liquid formulation available.  
• Dosing information for young infants available.  
• Can give with food  
• Extended-release formulation is available that allows for once-daily dosing in older children. | • Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen.  
• Higher incidence of rash/HSR than other NNRTIs  
• Higher rates of serious hepatic toxicity than EFV  
• Decreased virologic response compared with EFV  
• Twice-daily dosing necessary in children with BSA <0.58 m² |
### Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children

<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>RPV</td>
<td>• Once-daily dosing&lt;br&gt;• Available in a 1-pill-daily, fixed-dose combination tablet containing RPV/FTC/TDF (Complera) and RPV/FTC/TAF (Odefsey)&lt;br&gt;• 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>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 dual-NRTI backbone, targets HIV at 2 steps of viral replication (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 ritonavir boosting resulting in associated drug interactions.</td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>• Once-daily dosing&lt;br&gt;• Powder formulation available&lt;br&gt;• ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).&lt;br&gt;• Available in a fixed-dose combination tablet containing ATV/COBI (Evotaz) that reduces pill burden of a boosted PI regimen</td>
<td>• No liquid formulation&lt;br&gt;• Food effect (should be administered with food)&lt;br&gt;• Indirect hyperbilirubinemia is common but asymptomatic.&lt;br&gt;• Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG).&lt;br&gt;• RTV component associated with large number of drug interactions.</td>
<td></td>
</tr>
<tr>
<td>DRV/r</td>
<td>• Can be used once daily in children aged ≥12 years&lt;br&gt;• Liquid formulation available&lt;br&gt;• Available in a fixed-dose combination tablet containing DRV/COBI (Prezcobix) that reduces pill burden of a boosted PI regimen.</td>
<td>• Pediatric pill burden high with current tablet dose formulations&lt;br&gt;• Food effect (should be administered with food)&lt;br&gt;• Must be given with RTV boosting to achieve adequate plasma concentrations.&lt;br&gt;• Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown.&lt;br&gt;• RTV component associated with large number of drug interactions.&lt;br&gt;• Can only be used once-daily in absence of certain PI-associated resistance mutations.</td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>• LPV only available coformulated with RTV in liquid and tablet formulations.&lt;br&gt;• Tablets can be given without regard to food but may be better tolerated when taken with meal or snack.</td>
<td>• Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone.&lt;br&gt;• Food effect (liquid formulation should be administered with food).&lt;br&gt;• RTV component associated with large number of drug interactions.&lt;br&gt;• Should not be administered to neonates before a postmenstrual age (first day of the mother’s last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age ≥14 days.&lt;br&gt;• Must be used with caution in patients with preexisting conduction system defects (can prolong PR and QT interval of ECG).</td>
<td></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>
<tr>
<td>Dual-NRTI</td>
<td>ABC plus</td>
<td>• Palatable liquid formulations</td>
<td>• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.</td>
</tr>
<tr>
<td>Backbones</td>
<td>(3TC or FTC)</td>
<td>• Can give with food.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ABC and 3TC are coformulated as a single pill for older/larger patients weighing ≥25 kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Available as a fixed-dose combination tablet containing ABC/3TC/DTG (Triumeq) in a single, but large, tablet.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ddI plus</td>
<td>• Delayed-release capsules of ddI may allow once-daily dosing in children aged ≥6 years, weighing ≥20 kg, able to swallow pills, and who can receive adult dosing along with once-daily FTC.</td>
<td>• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be co-administered with FTC or 3TC).</td>
</tr>
<tr>
<td></td>
<td>(3TC or FTC)</td>
<td>• FTC available as a palatable liquid formulation administered once daily.</td>
<td>• Limited pediatric experience using delayed-release ddI capsules in younger children</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pancreatitis, lactic acidosis, neurotoxicity with ddI</td>
</tr>
<tr>
<td></td>
<td>TAF plus</td>
<td>• Once-daily dosing</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>FTC for adolescents ≥12 years</td>
<td>• Small tablet size</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Less tenofovir-associated renal and bone toxicity with TAF compared to TDF in adults</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TAF and FTC are coformulated as a single tablet (Descovy).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Available as fixed-dose combination tablets: EVG/COBI/FTC/TAF (Genvoya) and RPV/FTC/TAF (Odefsey)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF plus</td>
<td>• Once-daily dosing for TDF</td>
<td>• Limited pediatric experience</td>
</tr>
<tr>
<td></td>
<td>(3TC or FTC)</td>
<td>• Resistance is slow to develop.</td>
<td>• Potential bone and renal toxicity, toxicity may be less in post-pubertal children.</td>
</tr>
<tr>
<td></td>
<td>for adolescents, SMR IV or V</td>
<td>• Less mitochondrial toxicity than other NRTIs.</td>
<td>• Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can give with food.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Available as reduced-strength tablets and oral powder for use in younger children</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• TDF and FTC are coformulated as single tablet (Truvada) and available in multiple strengths.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Available as fixed-dose combination tablets: EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and RPV/FTC/TDF (Complera)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZDV plus</td>
<td>• Extensive pediatric experience</td>
<td>• Bone marrow suppression with ZDV</td>
</tr>
<tr>
<td></td>
<td>(3TC or FTC)</td>
<td>• ZDV and 3TC are coformulated as single pill for older/larger patients.</td>
<td>• Lipoatrophy with ZDV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Palatable liquid formulations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can give with food.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• FTC is available as a palatable liquid formulation administered once daily.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ZDV plus</td>
<td>• Palatable liquid formulations</td>
<td>• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.</td>
</tr>
<tr>
<td></td>
<td>ABC</td>
<td>• Can give with food.</td>
<td>• Bone marrow suppression and lipoatrophy with ZDV</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>
<tr>
<td>Dual-NRTI Backbones</td>
<td>ZDV plus ddl</td>
<td>• Extensive pediatric experience</td>
<td>• Bone marrow suppression and lipoatrophy with ZDV</td>
</tr>
<tr>
<td>In Alphabetical Order</td>
<td></td>
<td>• Delayed-release capsules of ddl may allow SMR dosing of ddl in older</td>
<td>• Pancreatitis, neurotoxicity, <strong>lactic acidosis</strong> with ddl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>children able to swallow pills and who can receive adult doses</td>
<td>• ddl liquid formulation is less palatable than 3TC or FTC liquid formulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bone marrow suppression and lipoatrophy with ZDV</td>
<td>• Food effect (ddl is recommended to be taken 1 hour before or 2 hours after food). Some</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pancreatitis, neurotoxicity, <strong>lactic acidosis</strong> with ddl</td>
<td>experts give ddl without regard to food in infants or when adherence is an issue.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ddl liquid formulation is less palatable than 3TC or FTC liquid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>formulation</td>
<td></td>
</tr>
</tbody>
</table>

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

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; DRV/r = darunavir/ritonavir; ddI = didanosine; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; 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; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; 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 for Being Not Recommended</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 ≥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></td>
<td>Potential for added toxicities</td>
</tr>
<tr>
<td>Dual NRTI combination of <strong>ABC</strong> plus <strong>ddI</strong></td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Dual NRTI combination of <strong>ABC</strong> plus <strong>TDF</strong></td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Regimens containing <strong>d4T</strong></td>
<td>Increased toxicities</td>
</tr>
<tr>
<td>Dual NRTI combination of <strong>TDF</strong> plus <strong>ddI</strong></td>
<td>Increase in concentrations; high rate of virologic failure</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>T20</strong>-containing regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td></td>
<td>Injectable preparation</td>
</tr>
<tr>
<td><strong>ETR</strong>-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td><strong>EVG</strong>-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td></td>
<td>Insufficient data to recommend regimens containing <strong>EVG</strong> except when administered as the fixed-dose combination tablet containing elvitegravir/ cobicistat/emtricitabine/TAF (Genvoya) in adolescents aged 12–18 and weighing ≥35 kg (see What to Start)</td>
</tr>
<tr>
<td><strong>FPV</strong>-based regimens</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td></td>
<td>Medication burden</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></td>
<td>Appropriate dose not determined in young infants</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><strong>GI</strong> intolerance</td>
</tr>
<tr>
<td></td>
<td>Metabolic toxicity</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></td>
<td>Appropriate dose has yet to be determined</td>
</tr>
<tr>
<td><strong>TPV</strong>-based regimens</td>
<td>Increased dose of <strong>RTV</strong> for boosting</td>
</tr>
<tr>
<td></td>
<td>Reported cases of intracranial hemorrhage</td>
</tr>
</tbody>
</table>

**Key to Abbreviations:** **ABC** = abacavir; **ARV** = antiretroviral; **ART** = antiretroviral therapy; **ATV** = atazanavir; **d4T** = stavudine; **ddI** = didanosine; **DRV** = darunavir; **EFV** = efavirenz; **ETR** = etravirine; **EVG** = elvitegravir; **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** = pharmacokinetic; **RTV** = ritonavir; **SQV** = saquinavir; **T20** = enfuvirtide; **TAF** = tenofovir alafenamide; **TDF** = tenofovir disoproxil fumarate; **TPV** = tipranavir
Table 10. ART Regimens or Components that Should Never Be 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 with combination including ≥3 ARV drugs  
• Monotherapy “holding” regimens associated with more rapid CD4 decline compared to non-suppressive ART | • Infants exposed to HIV (with negative viral testing) during 4- to 6-week period of prophylaxis to prevent perinatal transmission of HIV |
| **2 NRTIs Alone** | • Rapid development of resistance  
• Inferior antiviral activity compared with combination including ≥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 |

**ARV Components Never Recommended as Part of an ARV Regimen for Children**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Rationale</th>
<th>Exceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV plus IDV</td>
<td>• Potential additive hyperbilirubinemia</td>
<td>• No exceptions</td>
</tr>
<tr>
<td>Dual-NRTI Combinations:</td>
<td>• Enhanced toxicity</td>
<td>• No exceptions</td>
</tr>
<tr>
<td>• 3TC plus FTC</td>
<td>• Similar resistance profile and no additive benefit</td>
<td>• No exceptions</td>
</tr>
<tr>
<td>• d4T plus ZDV</td>
<td>• Antagonistic effect on HIV</td>
<td>• No exceptions</td>
</tr>
<tr>
<td>NVP as Initial Therapy in Adolescent Girls with CD4 Count &gt;250 cells/mm³ or Adolescent Boys with CD4 Count &gt;400 cells/mm³</td>
<td>• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups</td>
<td>• Only if benefit clearly outweighs risk</td>
</tr>
</tbody>
</table>
| Unboosted SQV, DRV, or TPV | • Poor oral bioavailability  
• Inferior virologic activity compared with other PIs | • No exceptions |

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; DRV = darunavir; EFV = efavirenz; 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 received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence</td>
<td>4 weeks of ZDV</td>
</tr>
</tbody>
</table>
| Higher Risk of Perinatal HIV Transmission\(^a,b\) | • 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\(^c\) | Combination ARV prophylaxis with 6 weeks ZDV and 3 doses of NVP (prophylaxis dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose)  
or  
Empiric HIV therapy consisting of ZDV, 3TC, and NVP (treatment dosage)\(^d\) |
| Presumed Newborn HIV Exposure           | Mothers with unknown HIV status who test 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).  
ARV management should be discontinued immediately if supplemental testing confirms that mother does not have HIV. |
| Newborn with Confirmed HIV\(^e\)        | Confirmed positive newborn HIV virologic test/NAT                           | 3 drug combination ARV regimen at treatment dosage               |

\(^a\) See text for evidence supporting combination ARV prophylaxis and empiric HIV therapy.  
\(^b\) 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 elevated viral load at delivery.  
\(^c\) Most experts would opt to administer empiric HIV therapy to infants with acute HIV during pregnancy because of the high risk for in utero infection. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.  
\(^d\) The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue NVP and/or 3TC after the return of negative newborn testing. ZDV should be continued for 6 weeks.  
\(^e\) Most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing.  

**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 8 for dosing specifics.

**Key to Acronyms:** 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP =
Table 12. Newborn Antiretroviral Dosing Recommendations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
</tr>
</thead>
</table>
| **ZDV** Treatment and Prophylaxis Dosage | >=35 Weeks’ Gestation at Birth  
Birth to Age 4–6 Weeks:  
• 4 mg/kg/dose orally twice daily  

**Simplified Weight-Band Dosing for Newborns >=35 Weeks:** |

<table>
<thead>
<tr>
<th>Weight Band (kg)</th>
<th>ZDV 10 mg/mL Oral Syrup Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;3 kg</td>
<td>1 mL</td>
</tr>
<tr>
<td>3 to &lt;4 kg</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>4 to &lt;5 kg</td>
<td>2 mL</td>
</tr>
</tbody>
</table>

>=30 to <35 Weeks’ Gestation at Birth  
Birth–Age 2 Weeks:  
• 2 mg/kg/dose orally twice daily  
Age 2 Weeks to 4–6 Weeks:  
• 3 mg/kg/dose orally twice daily  

<30 weeks’ Gestation at Birth  
Birth–Age 4 Weeks:  
• 2 mg/kg/dose orally twice daily  
Age 4–6 Weeks:  
• 3 mg/kg/dose orally twice daily  

**3TC** Treatment and Prophylaxis Dosage | >=32 Weeks’ Gestation at Birth:  
Birth–Age 4 Weeks:  
• 2 mg/kg/dose orally twice daily  
Age 4–6 Weeks:  
• 4 mg/kg/dose orally twice daily  

**NVP** Prophylaxis Dosage | Birth Weight 1.5–2 kg:  
• 8-mg dose orally once daily  
• **Note:** No calculation is required for this dose; **this is the actual dose, not a mg/kg dose.**  
Birth Weight >2 kg:  
• 12-mg dose orally once daily  
• **Note:** No calculation is required for this dose; **this is the actual dose, not a mg/kg dose.**  

**NVP** Treatment Dosage | >=37 Weeks’ Gestation at Birth  
Birth–Age 6 Weeks:  
• 6 mg/kg/dose orally twice daily  
34 to <37 Weeks’ Gestation at Birth  
Birth–Age 1 Week:  
• 4 mg/kg/dose orally twice daily  
Age 1–6 Weeks:  
• 6 mg/kg/dose orally twice daily  

**Key to Acronyms:** 3TC=lamivudine; IV= intravenous; NVP = nevirapine; ZDV = zidovudine
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.</td>
<td>Viral load monitoring should be done more frequently after initiating or changing medications.​</td>
</tr>
<tr>
<td>Assess quantitative self-report of missed doses.</td>
<td>Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).</td>
</tr>
<tr>
<td>Elicit description of medication regimen.</td>
<td>Ask patient and/or caregiver about the name/appearance, number, frequency of medications.</td>
</tr>
<tr>
<td>Assess barriers to medication administration.</td>
<td>Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.</td>
</tr>
<tr>
<td>Monitor pharmacy refills.</td>
<td>Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.</td>
</tr>
<tr>
<td>Conduct announced and unannounced pill counts.</td>
<td>Approaches include asking patients to bring medications to clinic, home visits, or referral to community health nursing.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeted Approaches to Monitor Adherence in Special Circumstances</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implement directly observed therapy.</td>
<td>Include brief hospitalization if indicated.</td>
</tr>
<tr>
<td>Measure plasma drug concentration.</td>
<td>Can be considered for particular drugs.​</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approaches to Monitor Medication Adherence in Research Settings</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure drug concentrations in hair.</td>
<td>Good measure of adherence over time.​</td>
</tr>
<tr>
<td>Use electronic monitoring devices.</td>
<td>Medication Event Monitoring System (MEMS) caps, Wisepill</td>
</tr>
<tr>
<td>Use mobile phone-based technologies.</td>
<td>Interactive voice response, SMS text messaging</td>
</tr>
</tbody>
</table>

​ See [Clinical and Laboratory Monitoring After Initiation of Combination Antiretroviral Therapy](https://www.aidsinfo.nih.gov/guidelines) (or [After a Change in Combination Antiretroviral Therapy](https://www.aidsinfo.nih.gov/guidelines)) regarding the frequency of adherence assessment after initiating or changing therapy.

​ See [Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection](https://www.aidsinfo.nih.gov/guidelines) regarding indications for therapeutic drug monitoring.

### Initial Intervention Strategies

- Establish trust and identify mutually acceptable goals for care.
- Obtain explicit agreement on the need for treatment and adherence.
- Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or caregiver that may decrease adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.
- Identify family, friends, health team members, and others who can support adherence.
- Educate patient and family about the critical role of adherence in therapy outcome including the relationship between partial adherence and resistance 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.
- 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.
- Establish readiness to take medication through practice sessions or other means.
- Schedule a home visit to review medications and determine how they will be administered in the home setting.
- Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.

### Medication Strategies

- Choose the simplest regimen possible, reducing dosing frequency and number of pills.
- When choosing a regimen, consider the daily and weekly routines and variations in patient and family activities.
- Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).
- Choose drugs with the fewest AEs; provide anticipatory guidance for management of AEs.
- Simplify food requirements for medication administration.
- Prescribe drugs carefully to avoid adverse drug-drug interactions.
- Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill swallowing cup, pill glide). Adjust pill size as needed.

### Follow-up Intervention Strategies

- Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.
- Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.
- Use patient education aids including pictures, calendars, and stickers.
- Encourage use of pill boxes, reminders, alarms, and timers.
- Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.
- Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
- Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.
- Consider DOT at home, in the clinic, or in selected circumstances, during a brief inpatient hospitalization.
- Consider gastrostomy tube use in selected circumstances.
- Information on other interventions to consider can be found at [http://www.cdc.gov/hiv/prevention/research/compendium/ma/complete.html](http://www.cdc.gov/hiv/prevention/research/compendium/ma/complete.html).

**Key to Acronyms:** 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 April 27, 2017; last reviewed April 27, 2017)*  
*(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>
</table>
| **Global CNS Depression** | LPV/r oral solution (contains both ethanol and propylene glycol as excipients) | Onset:  
• 1–6 days after starting LPV/r | Unknown, rare case reports | Prematurity  
Low birth weight  
Age <14 days (whether premature or term) | Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days. | 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). |

**Neuropsychiatric Symptoms and Other CNS Manifestations**  
EFV  

Onset:  
• 1–2 days after initiating treatment for many symptoms  
Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% experienced persistent symptoms at 12 months and in another, half of discontinuations occurred after 12 months.  
Presentation (May Include One 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)  

Variable, depending on age, symptom, assessment method  
Children:  
• 24% for any EFV-related CNS manifestations in 1 case series with 18% requiring drug discontinuation  
• 9% incidence of new-onset seizures reported in 1 study in children aged <36 months. In 2 of the children the seizures had alternative causes.  
• 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.  

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  

Administer EFV on an empty stomach, preferably at bedtime.  
Before starting EFV, obtain EFV trough concentration if symptoms excessive or persistent. If EFV trough concentration >4 mcg/mL, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).  
In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time.  

Obtain EFV trough concentration if symptoms excessive or persistent. If EFV trough concentration >4 mcg/mL, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).  
In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time.
### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity  
(Last updated April 27, 2017; last reviewed April 27, 2017)  (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 | EFV | • Cerebellar dysfunction (tremor, dysmetria, ataxia)  
**Note:** Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children. | | | | |
| | RPV | **Presentation**  
Neuropsychiatric Symptoms:  
• Depressive disorders  
• Suicidal ideation  
• Abnormal dreams/nightmares  
Other CNS Manifestations:  
• Headache  
• Dizziness  
• Insomnia  
• Somnolence | In 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.  
In Children:  
• Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years to 17 years. Severe depressive disorders were reported in 5.6% of patients, including a suicide attempt in 1 subject.  
• Somnolence reported in 5/36 (14%) children. | Prior history of neuropsychiatric illness | Monitor carefully for depressive disorders and other CNS symptoms. | Consider drug substitution in case of severe symptoms. |
| | RAL | **Presentation:**  
• Increased psychomotor activity  
• Headaches  
• Insomnia  
• Depression  
• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia) | Children:  
• Increased psychomotor activity reported in one child.  
Adults:  
• Headache  
• Insomnia (<5% in adult trials) | Elevated RAL concentrations  
Co-treatment with TDF or PPI or inhibitors of UGT1A1 | 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 case of severe insomnia or other neuropsychiatric symptoms. |
### Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity

 *(Last updated April 27, 2017; last reviewed April 27, 2017)*

<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>DTG</td>
<td>Onset: • 7–30 days after initiating drug</td>
<td>Neuropsychiatric Symptoms: • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation attempt, behavior, or completion</td>
<td>Adults: • Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common, reported in up to 10% of patients. Less than 1% of patients experienced more severe symptoms.</td>
<td>Pre-existing depression or other psychiatric illness</td>
<td>Use with caution in the presence of psychiatric illness, especially depression.</td>
<td>For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. Discontinuation resulted in resolution of neuropsychiatric symptom 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.</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>TPV</td>
<td>Onset: • 7–513 days after starting TPV</td>
<td>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.</td>
<td>Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported.</td>
<td>Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.</td>
<td>Discontinue TPV if ICH is suspected or confirmed.</td>
</tr>
</tbody>
</table>

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; PPI = proton pump inhibitor; py = patient years; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucuronyl transferase
Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>PIs: All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV. NRTIs: Especially d4T NNRTIs: EFV &gt; NVP, RPV, and ETR</td>
<td>Onset: As early as 2 weeks to months after beginning therapy Presentation: ↑LDL-C, TC, and TG PIs: ↑LDL-C, TC, and TG NNRTIs: ↑LDL-C, TC, and HDL-C NRTIs: ↑LDL-C, TC, and TG</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/RTV. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities.</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 • Avoid d4T Monitoring: Adolescents and Adults: • 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. Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors: • Obtain non-fasting 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. Children with Lipid Abnormalities and/or Additional Risk Factors: • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). ART regimen changes can be considered. Discontinue d4T or substitute a PI-sparing regimen or PI-based regimen with a more favorable lipid profile.</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. (^b) Counsel on lifestyle modification, dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars particularly in case of ↑TG, elimination of transfat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician. Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails. Some experts suggest treatment in 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. (^b) The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL, while maintaining viral control.</td>
</tr>
</tbody>
</table>
Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 27, 2017; last reviewed April 27, 2017) (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>Dyslipidemia, continued</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 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).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.</td>
<td></td>
</tr>
</tbody>
</table>

Statins such as pravastatin, atorvastatin, or rosuvastatin\(^c\) can be considered.\(^d\) 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.\(^c\) Statins may also increase the risk of insulin resistance and diabetes mellitus. Risks must be weighed against potential benefits. Cholesterol absorption inhibitors (e.g., ezetimibe) can be considered as alternative.

Drug therapy for severe hypertriglyceridemia \((TG \geq 500 \text{ mg/dL})\) 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.

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\(^a\) Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides from non-fasting blood samples and follow up abnormal values with a test done in the fasted state.


\(^c\) 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.

\(^d\) Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (exception pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosuvastatin (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 [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](https://aidsinfo.nih.gov/guidelines).
Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects  
(Last updated April 27, 2017; last reviewed April 27, 2017)

<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>
| Nausea/Vomiting | Principally ZDV and PIs, but can occur with all ARVs and COBI | Onset:  
• Early  
Presentation:  
• Nausea, emesis—may be associated with anorexia and/or abdominal pain. | Varies with ARV agent; 10% to 30% in some series | Unknown | Instruct patient to take PIs with food. Monitor for weight loss, ARV adherence. | Reassurance—generally improves over time (usually 6–8 weeks)  
Supportive care.  
Antiemetics may be useful in extreme or persistent cases. |
| Diarrhea | PIs (particularly NFV, LPV/r, FPV/r), buffered ddl, INSTIs (mild) | Onset:  
• Early  
Presentation:  
• Generally soft, more frequent stools | Varies with ARV agent; 10% to 30% in some series | Unknown | Monitor for weight loss, dehydration. | Exclude infectious causes of diarrhea if prolonged or severe.  
Reassurance—generally improves over time (usually 6–8 weeks)  
Although treatment data in children are lacking, potentially useful modalities include:  
• Dietary modification  
• Calcium carbonate (should not be used with DTG)  
• Bulk-forming agents (psyllium)  
• Antimotility agents (loperamide)  
• Crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults, but not in children. |
| Pancreatitis | ddl, d4T (especially concurrently), boosted PIs  
Reported, albeit rarely, with most ARVs. | Onset:  
• Any time, usually after months of therapy  
Presentation:  
• Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis). | <2% in recent series | Use of concomitant medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin)  
Hypertriglyceridemia  
Advanced disease  
Previous episode of pancreatitis  
Alcohol use | Avoid use of ddl in patients with a history of pancreatitis. | Discontinue offending agent—avoid reintroduction.  
Manage symptoms of acute episode.  
If associated with hypertriglyceridemia, consider interventions to lower TG levels. |

**Key to Acronyms:**  
ART = antiretroviral therapy; ARV = antiretroviral; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*
### Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects *(Last updated April 27, 2017; last reviewed April 27, 2017)*

<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> <em>a</em></td>
<td>ZDV</td>
<td>Onset:</td>
<td>Newborns Exposed to HIV:</td>
<td>Newborns Exposed to HIV:</td>
<td>Newborns Exposed to HIV:</td>
<td>Newborns Exposed to HIV:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variable, weeks to months</td>
<td>• Premature birth</td>
<td>• Obtain CBC at birth.</td>
<td>• Rarely requires intervention unless Hgb is &lt;7.0 g/dL or is associated with symptoms.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation</td>
<td>• Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir.</td>
<td>• 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).</td>
<td>• Consider discontinuing ZDV if 4 weeks or more of prophylaxis has been completed (see the Perinatal Guidelines*).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Most Commonly:</em></td>
<td>• Advanced maternal HIV</td>
<td>Children Living with HIV on ARVs:</td>
<td>Children Living with HIV on ARVs:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Asymptomatic or mild fatigue</td>
<td>• Neonatal blood loss</td>
<td>• Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency)</td>
<td>• Avoid ZDV in children with moderate to severe anemia when alternative agents are available.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pallor</td>
<td>• Combination ARV prophylaxis, particularly with ZDV plus 3TC</td>
<td>• Myelosuppressive drugs (e.g., TMP-SMX, rifabutin)</td>
<td>• Obtain CBC as part of routine care.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tachypnea</td>
<td>• Iron deficiency</td>
<td>• Advanced or poorly controlled HIV disease</td>
<td>Children Living with HIV on ARVs:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Rarely:</em></td>
<td>• Malnutrition</td>
<td><em>Avoid ZDV in children with moderate to severe anemia when alternative agents are available.</em></td>
<td><em>For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen.</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Congestive heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Macrocytosis</strong></td>
<td>ZDV; also d4T</td>
<td>Onset:</td>
<td>&gt;90% to 95%, all ages</td>
<td>None</td>
<td>Obtain CBC as part of routine care (see Laboratory and Clinical Monitoring section).</td>
<td>None required unless associated with anemia. D4T is no longer recommended and should be discontinued.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• Within days to weeks of starting therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MCV often &gt;100 fL</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td><em>Most often asymptomatic.</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Sometimes associated with anemia (occurs more often with ZDV than with d4T).</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects
(Last updated April 27, 2017; last reviewed April 27, 2017) (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>Neutropenia</td>
<td>ZDV</td>
<td>Onset:</td>
<td>Newborns Exposed to HIV:</td>
<td>Newborns Exposed to HIV:</td>
<td>Children Living with HIV on ARVs:</td>
<td>Newborns Exposed to HIV:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variable</td>
<td>• In utero exposure to ARVs</td>
<td>• Obtain CBC as part of routine care.</td>
<td>• No established threshold for intervention; some experts would consider using an alternative NRTI if ANC &lt;500 cells/mm³, or discontinue prophylaxis if ≥4 weeks of ZDV have been completed (see the <strong>Perinatal ARV Guidelines</strong>).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td>• Rare</td>
<td>• Combination ARV prophylaxis, particularly with ZDV plus 3TC, and myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)</td>
<td>Children Living with HIV on ARVs:</td>
<td>Children Living with HIV on ARVs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most commonly asymptomatic.</td>
<td>Children Living with HIV on ARVs:</td>
<td>• Advanced or poorly controlled HIV infection</td>
<td>• Discontinue non-ARV marrow-toxic drugs, if feasible.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 2.2% to 26.8% of children on ARVs, depending upon the ARV regimen.</td>
<td>• Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)</td>
<td>• Treat coexisting OIs and malignancies.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2% for ZDV/3TC</td>
<td>Children Living with HIV on ARVs:</td>
<td>• For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Highest rates with ZDV-containing regimens.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Key to Acronyms:**
- 3TC = lamivudine
- ANC = absolute neutrophil count
- ARV = antiretroviral
- CBC = complete blood count
- d4t = stavudine
- 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

**Notes:**
- a HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.
- b Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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

(Last updated April 27, 2017; last reviewed April 27, 2017)  (page 1 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>Hepatitis</td>
<td>• 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 all been associated with hepatitis in context of hypersensitivity reactions • NRTIs (especially ZDV, ddI, and d4T) have been associated with lactic acidosis and hepatic steatosis</td>
<td>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 co-infection may develop flare of hepatitis with the initiation of, withdrawal of, or development of resistance to 3TC, FTC, or TDF (especially if receiving only 1 anti-HBV agent). • Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-co-infection. Presentation: • Asymptomatic elevation of AST and ALT • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may present in context of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis.</td>
<td>Uncommon</td>
<td>HBV or HCV co-infection Other underlying liver disease Use of other hepatotoxic medications (e.g., St. John’s wort [Hypericum perforatum], Chaparral [Larrea tridentate], Germander [Teucrium chamaedrys]) Alcohol use Pregnancy For NVP-Associated Hepatic Events in Adults: • Female with pre-NVP CD4 count &gt;250 cells/mm³ • Male with pre-NVP CD4 count &gt;400 cells/mm³ • Population- specific HLA types • Higher drug concentrations for PIs, particularly TPV.</td>
<td>Prevention: • Avoid concomitant use of hepatotoxic medications. • If hepatic enzymes are elevated &gt;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., HBV- or HCV-co-infection or elevated baseline AST and ALT). For NVP: • Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months.</td>
<td>• Evaluate for other infectious and non-infectious causes and monitor closely. Asymptomatic: • Potentially offending ARVs should be discontinued if ALT or AST is &gt; 5x 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.</td>
</tr>
</tbody>
</table>
### Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

**Last updated April 27, 2017; last reviewed April 27, 2017**

<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>
| **Indirect Hyperbilirubinemia** | IDV, ATV (with either RTV or COBI) | Onset:  
• First months of therapy  
Presentation:  
• May be associated with jaundice or asymptomatic  
• 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 > 5x ULN and 1.4% experienced jaundice. | N/A | Monitoring:  
• No ongoing monitoring needed. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time. | • Isolated indirect hyperbilirubinemia is not indication for cessation of potentially offending ARV  
• Psychological impact of jaundice should be evaluated and alternative agents considered |
| **Non-Cirrhotic Portal Hypertension** | ddi, d4T | Onset:  
• Generally after years of therapy  
Presentation:  
• GI bleeding, esophageal varices, hypersplenism  
• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism)  
• Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis. | Rare | Prolonged exposure to ARV therapy, especially ddi and the combination of ddi and d4T | Monitoring:  
• No specific monitoring | • Discontinue potentially offending agents.  
• Manage complications of GI bleeding and esophageal varices. |

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

**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; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine
**Table 15f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus**

*(Last updated April 27, 2017; last reviewed April 27, 2017)*

<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</th>
<th>Monitoring</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Resistance, Asymptomatic Hyperglycemia, DM*</td>
<td>ZDV</td>
<td>Onset: Weeks to months after beginning therapy</td>
<td>Insulin Resistance</td>
<td>Risk Factors for Type 2 DM:</td>
<td>Counsel on lifestyle modification (e.g., a diet low in saturated fat, cholesterol, transfat, and refined sugars; increased physical activity; cessation of smoking); consultation with dietician.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>d4T</td>
<td></td>
<td>ARV-Treated Children:</td>
<td>• Lipodystrophy</td>
<td>Avoid ZDV, d4T, ddl when possible.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ddI</td>
<td></td>
<td>• 6% to 12%</td>
<td>• Metabolic syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LPV/r</td>
<td></td>
<td>Impaired Fasting Glucose</td>
<td>• Family history of DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IDV</td>
<td></td>
<td>ARV-Treated Children:</td>
<td>• High BMI (obesity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rarely other PIs</td>
<td></td>
<td>• 0% to 7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impaired Glucose Tolerance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ARV-Treated Children:</td>
<td>• 3% to 4%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DM</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ARV-Treated Children:</td>
<td>• 0.2 per 100-person-years</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 random and fasting plasma glucose 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; IDV = indinavir; 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
### Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis

(Last updated April 27, 2017; last reviewed April 27, 2017)

<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>
| **Lactic Acidosis** | NRTIs, in particular, d4T and ddI (highest risk when co-administered) | Onset:  
• 1–20 months after starting therapy (median onset 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  
| Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L)  
Adults:  
• 15% to 35% of adults receiving NRTI therapy for longer than 6 months  
Children:  
• 29% to 32%  
Symptomatic Severe Hyperlactatemia (>5.0 mmol/L)  
Adults:  
• 0.2% to 5.7%  
Symptomatic Lactic Acidosis/Hepatic Steatosis:  
• Rare in all age groups (1.3–11 episodes per 1000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%)  
Adults:  
• Female gender  
• 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 <350 cells/mm³  
• Acquired riboflavin or thiamine deficiency  
• Possibly pregnancy  
Preterm Infants or Any Neonates before Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days has Been Attained:  
• Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution) due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events.  
| Prevention:  
• d4T and ddI should both be avoided individually; co-administration of d4T and ddI is contraindicated (no exception).  
• Due to the presence of propylene glycol as a diluent, LPV/r oral solution should not be used in preterm neonates or any neonate before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days has been attained.  
• Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.  
Monitoring  
Asymptomatic:  
• Measurement of serum lactate is not recommended.  
Clinical Signs or Symptoms Consistent with Lactic Acidosis:  
• Obtain blood lactate level.  
 Additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.  
| Lactate 2.1–5.0 mmol/L (Confirmed with Second Test):  
• Replace ddI and d4T with other ARVs.  
• As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.  
Lactate >5.0 mmol/L (Confirmed with Second Test) or >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 an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC), and monthly monitoring of lactate for at least 3 months.  

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**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; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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### Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy  *(Last updated April 27, 2017; last reviewed April 27, 2017)* (page 1 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>Lipodystrophy (Fat Maldistribution) General Information</td>
<td>See below for specific associations.</td>
<td>Onset: • Trunk and limb fat initially increase; peripheral fat wasting may not appear for 12 to 24 months after ART initiation.</td>
<td>Varies greatly depending upon measure and comparator group.</td>
<td>Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus</td>
<td>See below.</td>
<td>A regimen review with consideration of changing the regimen should be considered, whenever present. Improvement following regimen change is variable, may take months to several years, or may not occur at all.</td>
</tr>
<tr>
<td>Central Lipohypertrophy or Lipoaccumulation</td>
<td>Can occur in the absence of ART, but most associated with PIs and EFV.</td>
<td>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.</td>
<td>Adults: • Up to 93% Children: • Up to 34%</td>
<td>Obesity before initiation of therapy Sedentary lifestyle</td>
<td>Prevention: • Calorically appropriate low-fat diet and exercise Monitoring: • BMI measurement • Body circumference and waist-hip ratio</td>
<td>Calorically appropriate healthy diet low in saturated fats and simple carbohydrates, and exercise, especially strength training Smoking cessation (if applicable) to decrease future CVD risk Consider switching 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</td>
</tr>
</tbody>
</table>
Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy  *(Last updated April 27, 2017; last reviewed April 27, 2017)*

<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 decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.</td>
<td>Adults: • Up to 59% Children: • Up to 47% • Risk lower (up to 15%) in patients not treated with d4T or ZDV.</td>
<td>Underweight before ART</td>
<td>Prevention: • Avoid use of d4T and ZDV. Monitoring: • Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.</td>
<td>Replace d4T (no longer recommended) or ZDV with other NRTIs if possible. 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
### Table 15i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects
(Last updated April 27, 2017; last reviewed April 27, 2017)  (page 1 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>
| Urolithiasis/ Nephrolithiasis | ATV, IDV, DRV | Onset:  
• Weeks to months after starting therapy  
Clinical Findings:  
• Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine  
ATV-related nephrolithiasis occurs in <10%.  
IDV-related higher (29%) in children than adults (12.4%)  
Unknown in children | In adults, elevated urine pH (>5.7) | | | Provide adequate hydration and pain control; consider using alternative ARV. If on IDV, discontinue. |
| Renal Dysfunction | TDF | Onset:  
• Variable; in adults, weeks to months after initiation of therapy.  
• Hypophosphatemia appears at a median of 18 months.  
• Glucosuria may have onset after a year of therapy.  
• Abnormal urine protein/osmolality ratio may be an early indicator.  
More Common:  
• Increased serum creatinine, proteinuria, normoglycemic glucosuria.  
• Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness.  
Less Common:  
• Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria  
Adults:  
• Approximately 2% with increased serum creatinine  
• Approximately 0.5% with severe renal complications  
Children:  
• Approximately 4% with hypophosphatemia or proximal tubulopathy; higher with prolonged TDF therapy, in advanced HIV infection or concomitant use of ddl | Adults:  
• Approximately 2% with increased serum creatinine  
• Approximately 0.5% with severe renal complications  | Risk May Be Increased in Children with:  
• Age >6 years  
• Black race, Hispanic/Latino ethnicity  
• Advanced HIV infection  
• Hypertension  
• Diabetes  
• Concurrent use of ddl or PIs (especially LPV/r), and preexisting renal dysfunction  
• Risk increases with longer duration of TDF treatment | Monitor urine protein and 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. In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also measure serum phosphate. Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time.  
If TDF is the likely cause, consider using alternative ARV. TAF has significantly less toxicity than TDF. |

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### Table 15i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

_Last updated April 27, 2017; last reviewed April 27, 2017_ (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:</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 increases are ongoing with time.</td>
<td>No need to change therapy. Reassure patient about the benign nature of the laboratory abnormality.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Within a month of starting treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in eGFR.</td>
<td></td>
<td></td>
<td></td>
<td></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 = boosted lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
### Table 15j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis  
(Last updated April 27, 2017; last reviewed April 27, 2017)

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestations</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
</tr>
</thead>
</table>
| Osteopenia and Osteoporosis | Any ART regimen | Onset: • Any age; decrease in BMD usually seen early after initiation of ART.  
Presentation: • Most commonly asymptomatic  
• Rarely presents as osteoporosis; a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma). | BMD z Score Less Than -2.0  
• <10% in U.S. cohorts  
• Approximately 20% to 30% in international cohorts | Longer duration and greater severity of HIV disease  
Growth or pubertal delay  
Low BMI  
Lipodystrophy  
Non-black race  
Smoking  
Prolonged systemic corticosteroid use  
Medroxyprogesterone use  
Limited weight-bearing exercise | 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).  
Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories).  
• Consider measuring serum 25-OH-vitamin D level.  
• DXA.  
Same options as for prevention.  
Consider change in ARV regimen (e.g., changing TDF to TAF).  
Role of bisphosphonates not established in children with HIV infection. |

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a Some experts would periodically measure 25-OH-vitamin D, especially in urban youth with HIV infection, because in that population, the prevalence of vitamin D insufficiency is high.

b Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for prepubertal children and children in early puberty who are initiating treatment with TDF. DXA could also be considered in adolescent women on TDF and medroxyprogesterone and in 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; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate; TAF = tenofovir alafenamide
Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity  *(Last updated April 27, 2017; last reviewed April 27, 2017)*

<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>ARV Toxic Neuropathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>d4T, ddl PIs</td>
<td>Onset: Weeks to months  Presentation:  • Decreased sensation  • Aching, burning, painful numbness  • Hypalgesia  • Allodynia  • Decreased or absent ankle reflexes  Distribution:  • Bilateral soles of feet, ascending to legs and fingertips</td>
<td>Children:  • Around 1% overall  • d4T—10% to 25%  Adults:  • d4T—up to 50%</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>Avoid use of d4T and ddl.  Monitor for symptoms and signs of peripheral neuropathy.</td>
<td>Discontinue offending agent.  Topical capsaicin 8% may be helpful.  Consider referral to a neurologist.  Data are insufficient to allow the Panel to recommend use of any of the following modalities: tricyclic antidepressants, gabapentin, pregabalin, mexiletine, Lamotrigine, and acupuncture or other complementary approaches</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; ddl = didanosine; INH = isoniazid; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor
### Table 151. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  
(Last updated April 27, 2017; last reviewed April 27, 2017)  
(page 1 of 4)

<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 therapy  
Presentation:  
• Most rashes are mild-to-moderate, diffuse maculopapular eruptions.  
**Note:** A rash can be the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major) | 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). a  
• 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 will resolve without intervention; ARVs can be continued while monitoring. a  
• Antihistamines may provide some relief.  
Severe Rash (e.g., Blister, 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). |  |
| **ENF** | | Onset:  
• First few days to weeks after starting therapy  
Presentation:  
• Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time | Adults and Children:  
• >90% |  | Routinely assess patient for local reactions.  
• Rotate injection sites.  
• Massage area after injection. |  |

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Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Table 15I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  
(Last updated April 27, 2017; last reviewed April 27, 2017)  

<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 initiating therapy  
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 such as 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 with one NNRTI, many experts would avoid use of other NNRTIs. |
| DRESS | EFV, ETR, NVP, RAL, RPV, DRV | Onset:  
1–8 weeks  
Presentation:  
Fever  
Lymphadenopathy  
Facial swelling  
Morbilliform to polymorphous rash  
Peripheral eosinophilia  
Atypical circulating lymphocytes  
Internal organ involvement (particularly liver and/or renal) | Rare | Unknown | • Obtain CBC, AST, ALT and creatinine in patient presenting with suggestive symptoms. | • Discontinue all ARVs and other possible causative agents such as TMP-SMX.  
Role for steroids unclear; suggest consultation with specialist.  
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 April 27, 2017; last reviewed April 27, 2017)*

<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>HSR</td>
<td>ABC</td>
<td>Onset</td>
<td>2.3% to 9% (varies by racial/ethnic group).</td>
<td>HLA-B<em>5701 (HSR very uncommon in people who are HLA-B</em>5701-negative); also HLA-DR7, HLA-DQ3.</td>
<td>• Screen for HLA-B<em>5701. **ABC should not be prescribed if HLA-B</em>5701 is present.** The medical record should clearly indicate that ABC is contraindicated.</td>
<td>• Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness). <strong>If ABC is contraindicated.</strong> • Treat symptoms as necessary. • Most symptoms resolve within 48 hours after discontinuation of ABC. • Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.</td>
</tr>
<tr>
<td>HSR With or without skin involvement and excluding SJS/TEN</td>
<td>**</td>
<td>Onset With First Use: • Within first 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**</td>
<td>With Reintroduction: • Within hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>**</td>
<td>Presentation: • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea). • Symptoms worsen to include hypotension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 15I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions  (Last updated April 27, 2017; last reviewed April 27, 2017) (page 4 of 4)

<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>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>
<tr>
<td></td>
<td></td>
<td>• Most frequent in the first few weeks of therapy but can occur through 18 weeks.</td>
<td></td>
<td>• Treatment-naive with higher CD4 count (&gt;250 cells/mm$^3$ in women; &gt;400 cells/mm$^3$ in men).</td>
<td>• 2-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce risk of reaction.$^{a}$</td>
<td>Consider other causes for hepatitis and discontinue all hepatotoxic medications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td>• Female gender (risk is 3-fold higher in females compared with males).</td>
<td>• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.</td>
<td>Provide supportive care as indicated and monitor patient closely</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy.</td>
<td></td>
<td>Children:</td>
<td>• NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 &lt;15%.</td>
<td>Do not re-introduce NVP.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 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.</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Avoid NVP use in women with CD4 counts &gt;250 cells/mm$^3$ and in men with CD4 counts &gt;400 cells/mm$^3$ unless benefits outweigh risks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Do not use NVP in PEP.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ENF, ETR</td>
<td>Onset:</td>
<td>Rare</td>
<td>Unknown</td>
<td>Evaluate for hypersensitivity if the patient is symptomatic.</td>
<td>• Discontinue ARVs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Any time during therapy.</td>
<td></td>
<td></td>
<td>• Rechallenge with ENF or ETR is not recommended.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Presentation:</td>
<td></td>
<td></td>
<td>• Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure.</td>
<td></td>
</tr>
<tr>
<td></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></td>
<td></td>
<td></td>
<td></td>
<td>• Rechallenge with MVC is not recommended.</td>
<td></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>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rechallenge with DTG is contraindicated.</td>
<td></td>
</tr>
</tbody>
</table>
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 consultation with an expert in HIV care should be obtained. **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 cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; 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; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine.
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 Regimens* (page 1 of 2)

<table>
<thead>
<tr>
<th>ARV Drug(s)</th>
<th>Age</th>
<th>Body Size Attained</th>
<th>Potential ARV Regimen Change</th>
<th>Comment[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>≥1 year</td>
<td>Any</td>
<td>ABC once daily</td>
<td>See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for full discussion.</td>
</tr>
<tr>
<td>Twice Daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZDV or ddI</td>
<td>≥1 year</td>
<td>N/A</td>
<td>ABC</td>
<td>Once-daily dosing (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Less long-term mitochondrial toxicity. TDF is a reasonable option for children unable to take ABC (HLA B5701 positive) who want to switch to a once-daily regimen.</td>
</tr>
<tr>
<td>or d4T[^c]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;35 kg</td>
<td>TAF or ABC</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Adolescence</td>
<td>Pubertal maturity (i.e., SMR IV or V)</td>
<td>TDF, TAF or ABC</td>
<td>Once-daily dosing. Less long-term mitochondrial toxicity. Coformulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone toxicity.</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>≥12 years</td>
<td>≥40 kg</td>
<td>ATV/r DRV/r DTG</td>
<td>Smaller pill (DTG), higher barrier to resistance given concern for adherence challenges developing in adolescents.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RPV</td>
<td>DRV/r may be administered once daily in children aged ≥12 years without DRV resistance mutations.</td>
</tr>
<tr>
<td>ARV Drug(s)</td>
<td>Age</td>
<td>Body Size Attained</td>
<td>Potential ARV Regimen Change</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td>-------------------</td>
<td>------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LPV/r</td>
<td>≥1 year</td>
<td>≥3 kg</td>
<td>RAL</td>
<td>Better palatability. Less adverse lipid effect. Lower pill burden. Once-daily dosing (ATV/r).</td>
</tr>
<tr>
<td></td>
<td>≥3 years</td>
<td>N/A</td>
<td>ATV/r</td>
<td>Once-daily dosing (EFV and ATV/r). Better palatability. Less adverse lipid effect. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children aged &lt;3 years.</td>
</tr>
<tr>
<td></td>
<td>≥12 years</td>
<td>≥40 kg</td>
<td>DRV/r, ATV/r, DTG</td>
<td>Once-daily dosing possible. Lower pill burden.</td>
</tr>
</tbody>
</table>
| Other       | Adolescence |                   | For regimens with TDF: pubertal maturity (i.e., SMR IV or V) | Co-formulated:  
|             |           |                   | TDF/FTC/EFV, TDF/FTC/EVG/Cobi (weighing ≥35 kg), TDF/FTC/RPV, TAF/FTC/RPV (weighing ≥35 kg), ABC/3TC/DTG (weighing ≥40 kg), TAF/FTC plus DTG | Once-daily dosing. Single pill. Alignment with adult regimens. TAF/FTC plus DTG may be more desirable because of small pill sizes even though it increases pill burden to 2 pills instead of 1. TAF-based regimens can be used with adolescents weighing ≥35 kg. Use ABC/3TC/DTG for adolescents weighing ≥40 kg |

*This list is not exhaustive in that it does not necessarily list all potential options, but instead, shows examples of what kinds of changes can be made.*

*b* Comments relevant to the potential ARV change listed. Does not include all relevant information. Please refer to individual drug tables for full information.

*c* Because of concerns about long-term adverse events, d4T should be replaced with a safer drug even before sustained virologic suppression is achieved (see Stavudine in Appendix A: Pediatric Antiretroviral Drug Information).

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; Cobi = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; 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 (Tanner stage); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; 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., immunologic response not actually poor)
- Low pretreatment CD4 cell count or percentage
- Adverse effects of use of ZDV or the combination of TDF and didanosine
- Use of systemic corticosteroids or chemotherapeutic agents
- Conditions that can cause low CD4 values, such as HCV, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis

Poor Immunologic and Clinical Responses Despite Virologic Suppression:
- Lab error
- Falsely low viral load result for HIV strain/type 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 tuberculosis
- Malignancy

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

- IRIS
- Previously unrecognized preexisting 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
- HCV = hepatitis C virus
- IRIS = immune reconstitution inflammatory syndrome
- TB = tuberculosis
- TDF = tenofovir disoproxil fumarate
- ZDV = zidovudine

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Table 17. Discordance Among Virologic, Immunologic, and Clinical Responses

<table>
<thead>
<tr>
<th>Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression</th>
<th>Diff. Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:</td>
<td>Poor Immunologic and Clinical Responses Despite Virologic Suppression:</td>
</tr>
<tr>
<td>• Lab error (in CD4 or viral load result)</td>
<td>• Lab error</td>
</tr>
<tr>
<td>• Misinterpretation of normal, age-related CD4 decline (i.e., immunologic response not actually poor)</td>
<td>• Falsely low viral load result for HIV strain/type not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2)</td>
</tr>
<tr>
<td>• Low pretreatment CD4 cell count or percentage</td>
<td>• Persistent immunodeficiency soon after initiation of ART but before ART-related reconstitution</td>
</tr>
<tr>
<td>• Adverse effects of use of ZDV or the combination of TDF and didanosine</td>
<td>• Primary protein-calorie malnutrition</td>
</tr>
<tr>
<td>• Use of systemic corticosteroids or chemotherapeutic agents</td>
<td>• Untreated tuberculosis</td>
</tr>
<tr>
<td>• Conditions that can cause low CD4 values, such as HCV, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis</td>
<td>• Malignancy</td>
</tr>
</tbody>
</table>

**Key to Acronyms:**
- ART = antiretroviral therapy
- CD4 = CD4 T lymphocyte
- 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&lt;sup&gt;a&lt;/sup&gt;</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 different RTV-boosted PI  
| | • INSTI plus different RTV-boosted PI +/- NNRTI +/- NRTI(s) |
| 2 NRTIs plus INSTI | • 2 NRTIs plus RTV-boosted PI  
| | • DTG (if not used in the prior regimen) + RTV-boosted PI +/- 1-2 NRTIs |
| Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s) | • INSTI + 2 NRTIs (if NRTIs are fully active)  
| | • INSTI + 2 NRTIs + RTV-boosted PI (if NRTIs are not fully active)  
| | • INSTI + RTV-boosted PI plus +/- ETR or RPV +/- NRTI(s) (if minimal NRTI activity) (consider adding T20 and/or MVC if additional active drug[s] needed) |

<sup>a</sup> ARV 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 2, but preferably 3, fully active drugs for durable, 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 adjustment when devising a regimen for children with multi-class drug resistance. Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class 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; T20 = enfuvirtide
Table 19. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Plasma Trough Concentration (ng/mL) ± Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>2,000±1,000</td>
</tr>
<tr>
<td>Darunavir</td>
<td>2,200±1,100</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>2,100</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>5,500±4,000</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>700±400</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1,700±1,000</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>4,500±1,900</td>
</tr>
<tr>
<td>Etravirine</td>
<td>300</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>20,000–45,000</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>65</td>
</tr>
</tbody>
</table>