Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Many additional antiretroviral (ARV) agents and combinations are available; some are not recommended for initial therapy, although they may be used in treatment-experienced children. This section describes ARV drugs and drug combinations that are not recommended for initial therapy for which data are insufficient to recommend use for initial therapy in ARV-naive children.

**Not Recommended**

These include drugs and drug combinations that are not recommended for initial therapy in ARV-naive children because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), pharmacologic antagonism, or better options within a drug class. These drugs and drug combinations are listed in Table 9.

**Insufficient Data to Recommend**

Drugs and drug combinations approved for use in adults that have insufficient, limited, and/or no pharmacokinetic (PK) or safety data for children cannot be recommended as initial therapy in children. However, these drugs and drug combinations may be appropriate to consider when managing treatment-experienced children (see Management of Children Receiving Antiretroviral Therapy). These drugs are also listed in Table 9.

**Antiretroviral Drugs and Combinations Not Recommended for Initial Therapy**

In addition to the regimens listed below, several ARV drugs, including tenofovir disoproxil fumarate (TDF) given to children aged <2 years, once-daily dosing of lopinavir/ritonavir (LPV/r), and full-dose ritonavir, are not recommended for use as initial therapy.

**Atazanavir without Ritonavir Boosting**

Although unboosted atazanavir is Food and Drug Administration (FDA)-approved for use in treatment-naive adolescents aged ≥13 years and weighing >39 kg who are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m2 basis) are required in adolescents than in adults to achieve adequate drug concentrations.1 The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend using atazanavir without ritonavir boosting because of these findings.

**Enfuvirtide-Based Regimens**

Enfuvirtide, a fusion inhibitor, is FDA-approved for use in combination with other ARV drugs to treat children aged ≥6 years who have evidence of HIV replication despite ongoing antiretroviral therapy (ART) (i.e., treatment-experienced children on non-suppressive regimens). Enfuvirtide must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Enfuvirtide is not recommended as initial therapy.

**Fosamprenavir-Based Regimens**

Fosamprenavir (the prodrug of amprenavir) is available in a pediatric liquid formulation and a tablet formulation, and has been investigated in children both with and without ritonavir boosting; it was approved by the FDA in June 2007 for use in patients aged ≥2 years.2-5 Fosamprenavir-containing regimens are not recommended for initial therapy because the volume of liquid medication when administered in the suspension form (without ritonavir boosting) needed is associated with vomiting in young children. There are also more advantageous boosted-protease inhibitor (PI) agents available. In addition, low levels of exposure may result in selection of resistance mutations that are associated with darunavir resistance.

**Indinavir-Based Regimens**

Although adequate virologic and immunologic responses have been observed with indinavir-based regimens...
in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis have been reported in pediatric patients using indinavir. Therefore, indinavir used alone or with ritonavir boosting is not recommended as initial therapy in children.

**Nelfinavir-Based Regimens**

The pediatric experience with nelfinavir-based regimens in ARV-naive and ARV-experienced children is extensive, with follow-up in children receiving the regimen continuing for as long as 7 years. The drug has been well tolerated; diarrhea is the primary adverse effect. However, in clinical studies, the virologic potency of nelfinavir has varied greatly. The optimal dose of nelfinavir in younger children, particularly in those aged <2 years, has not been well defined. Data in adults show inferior potency of nelfinavir compared with ritonavir-boosted PIIs, integrase strand transfer inhibitors (INSTIs), and efavirenz. For these reasons, the Panel does not recommend nelfinavir as initial therapy in children.

**Regimens Containing Only Nucleoside Reverse Transcriptase Inhibitors**

In adult trials, regimens containing only nucleoside reverse transcriptase inhibitors (NRTIs) have shown less potent virologic activity when compared with more potent non-nucleoside reverse transcriptase inhibitor (NNRTI) or PI-based regimens. Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited; in small observational studies, response rates of 47% to 50% have been reported. In a study on the use of the triple-NRTI regimen abacavir, lamivudine, and zidovudine in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining viral loads of <400 copies/mL at 48 weeks of treatment. Therefore, regimens containing only NRTIs are not recommended. A possible exception to this recommendation is the treatment of young children (aged <3 years) with concomitant HIV and tuberculosis for whom a nevirapine-based regimen is not acceptable. For these children, where treatment choices are limited, the World Health Organization recommends the use of a triple-NRTI regimen.

**Regimens Containing Three Drug Classes**

Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI or INSTI plus NRTI plus PI/NNRTI). Although studies of regimens containing three classes of drugs have demonstrated that these regimens are safe and effective in previously treated children and adolescents, these regimens have not been studied as initial therapy in treatment-naive children and adolescents and have the potential for inducing resistance to three drug classes, which could severely limit future treatment options. Ongoing studies, however, are investigating the use of three drug classes as treatment in neonates.

**Regimens Containing Three NRTIs and an NNRTI**

Data are currently insufficient to recommend a regimen of three NRTIs plus an NNRTI in young infants. A recent review of nine cohorts from 13 European countries suggested superior responses to this four-drug regimen when compared to boosted-PI or three-drug NRTI regimens. There has been speculation that poor tolerance and poor adherence to a PI-based regimen may account for differences. The ARROW trial, conducted in Uganda and Zimbabwe, randomized 1,206 children (median age 6 years) to receive either a standard NNRTI-based three-drug regimen or a four-drug regimen (three NRTIs and one NNRTI). After a 36-week induction period, the children on the four-drug regimen continued treatment on a dual-NRTI plus NNRTI regimen or an all-NRTI regimen. Although early benefits in CD4 T lymphocyte (CD4) improvement and virologic control were observed in the four-drug arm, these benefits were not sustained after de-intensification to the three-NRTI arm. Furthermore, after a median of 3.7 years on therapy, children in the initial four-drug arm who changed to an all-NRTI regimen had significantly poorer virologic control. Based on demonstrated benefits of recommended three-drug regimens and lack of additional efficacy data on the four-drug regimen, the Panel does not currently recommend this regimen.

**Saquinavir/Ritonavir**

A saquinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes to a
LPV/r-based regimen when used as initial therapy in treatment-naive adults. However, saquinavir is not recommended for initial therapy in children because the agent is not available in a pediatric formulation, and dosing and outcome data on saquinavir use in children are limited.

**Tipranavir-Based Regimens**

Tipranavir has been studied in treatment-experienced children and adults. This agent is a PI licensed for use in children aged ≥2 years. Tipranavir-based regimens are not recommended because high doses of ritonavir must be used to boost tipranavir and rare, but serious, cases of intracranial hemorrhage have been reported.

**Antiretroviral Drugs and Combinations with Data Insufficient to Recommend for Initial Therapy in Children**

Several ARV drugs and drug regimens are not recommended for initial therapy in ARV-naive children or for specific age groups because of insufficient pediatric data. These include the dual-NRTI backbone combinations abacavir/didanosine and abacavir/TDF. In addition, several new agents appear promising for use in adults but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. In addition, some dosing schedules may not be recommended in certain age groups based on insufficient data. As new data become available, these agents may become recommended agents or regimens. These agents and regimens are summarized below and are also listed in Table 9.

**Darunavir with Low-Dose Ritonavir Administered Once Daily (for Children Aged ≥3 to 12 Years)**

Data are limited on PK of once-daily darunavir/ritonavir (DRV/r) in young children. While modeling studies identified a once-daily dosing regimen that is now FDA-approved, the Panel is concerned about the lack of efficacy data for individuals aged ≥3 to <12 years treated with once-daily DRV/r. Therefore, once-daily dosing for initial therapy is not recommended in this age group. For children aged ≥3 to <12 years, twice-daily DRV/r is a preferred PI regimen. For older children who have undetectable viral loads on twice-daily therapy with DRV/r, practitioners can consider changing to once-daily treatment to make this regimen easier to use and support adherence if no darunavir-associated resistance mutations are present.

**Efavirenz for Children Aged ≥3 Months to 3 Years**

Efavirenz is FDA-approved for use in children aged ≥3 months and weighing ≥3.5 kg. Concerns regarding variable PK of the drug in the very young have resulted in a recommendation to not use efavirenz in children aged <3 years at this time (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). When use of efavirenz is being considered for children aged <3 years, CYP2B6 genotyping that predicts efavirenz metabolic rate should be performed, if available. Therapeutic drug monitoring can also be considered.

**Etravirine-Based Regimens**

Etravirine is an NNRTI that has been studied in treatment-experienced children aged ≥6 years. It is associated with multiple interactions with other ARV drugs, including tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, and unboosted PIs, and must be administered twice daily. Studies in treatment-experienced younger children are under way. It is unlikely that etravirine will be studied in treatment-naive children.

**Maraviroc-Based Regimens**

Maraviroc is an entry inhibitor that is FDA-approved for use in children aged ≥2 years and weighing ≥10 kg who have CCR5-tropic HIV-1 infection. It has been used infrequently in children. A dose-finding study in treatment-experienced children aged 2 to 18 years is enrolling patients in four age cohorts using both liquid and tablet formulations. Initial dose is based on body surface area and scaled from recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP450 3A4 inhibitor or inducer. The drug has multiple drug interactions and must be administered twice daily. In addition, tropism assays must be performed prior to use to ensure the presence of only CCR5-tropic virus.
**Antiretroviral Drug Regimens That Should Never Be Recommended**

Several ARV drugs and drug regimens should never be recommended for use in therapy of children or adults. These are summarized in Table 10. Clinicians should be aware of the components of fixed-dose drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination. The Panel no longer recommends the use of didanosine or stavudine as part of any ARV regimen. Didanosine and stavudine—given individually or together—should never be used due to the significant toxicities of these drugs and the availability of safer agents. Co-administration of stavudine and didanosine in an ARV regimen is contraindicated (with no exceptions) due to the enhanced toxicity of this combination. The combination of stavudine and didanosine has been linked to cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis in women who received this combination during pregnancy.29,30

Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children

<table>
<thead>
<tr>
<th>Regimen or ARV Component</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unboosted ATV-containing regimens in children</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td>DRV-based regimens once daily in children aged ≥3 to 12 years</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Unboosted DRV</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>Dual-NRTI combination of ABC plus TDF</td>
<td>Potential for added toxicities</td>
</tr>
<tr>
<td>EFV-based regimens for children aged &lt;3 years</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>T-20-containing regimens</td>
<td>Appropriate dose not determined</td>
</tr>
<tr>
<td>ETR-based regimens</td>
<td>Injectable preparation</td>
</tr>
<tr>
<td>FPV-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>IDV-based regimens</td>
<td>Reduced exposure</td>
</tr>
<tr>
<td>LPV/r dosed once daily</td>
<td>Medication burden</td>
</tr>
<tr>
<td>MVC-based regimens</td>
<td>Renal toxicities</td>
</tr>
<tr>
<td>NFV-based regimens</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Regimens containing only NRTIs</td>
<td>Variable PK</td>
</tr>
<tr>
<td>Regimens containing only NNRTIs</td>
<td>Appropriate dose not determined in young infants</td>
</tr>
<tr>
<td>Regimens containing 3 drug classes</td>
<td>Inferior virologic efficacy</td>
</tr>
<tr>
<td>Full-dose RTV or use of RTV as the sole PI</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Regimens containing 3 NRTIs and 1 NNRTI</td>
<td>GI intolerance</td>
</tr>
<tr>
<td>SQV-based regimens</td>
<td>Metabolic toxicity</td>
</tr>
<tr>
<td>TDF-containing regimens in children aged &lt;2 years</td>
<td>Added cost and complexity outweighs any benefit</td>
</tr>
<tr>
<td>TPV-based regimens</td>
<td>Limited dosing and outcome data</td>
</tr>
<tr>
<td>Reported cases of intracranial hemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; DRV = darunavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV/r = lopinavir/ ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetics; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

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

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Table 10. ART Regimens or Components Never Recommended for Treatment of HIV Infection in Children

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

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; CD4 = CD4 T lymphocyte; d4T = stavudine; ddi = didanosine; DRV = darunavir; FTC = emtricitabine; IDV = indinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; SQV = saquinavir; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ZDV = zidovudine

References
3. Cunningham C, Freedman A, Read S, et al. Safety and antiviral activity of fosamprenavir-containing regimens in...


