



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

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## What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated March 1, 2016; last reviewed March 1, 2016)

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 or 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 for consideration in management of 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 ARVs, including tenofovir disoproxil fumarate (TDF) in 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 treatment-naive adolescents aged  $\geq 13$  years who weigh  $>39$  kg and are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a  $\text{mg}/\text{m}^2$  basis) are required in adolescents than in adults to achieve adequate drug concentrations.<sup>1</sup> The Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel) does not recommend 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  $\geq 6$  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, has been investigated in children both with and without ritonavir boosting, and was approved by the FDA in June 2007 for use in pediatric patients aged  $\geq 2$  years.<sup>2-5</sup> Fosamprenavir-containing regimens are not recommended for initial therapy because of the volume of liquid medication when administered in the suspension form in young children without ritonavir boosting and associated vomiting, and availability of more advantageous boosted-protease inhibitor (PI) agents. 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.<sup>6-9</sup> Therefore, indinavir 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.<sup>10</sup> 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 showing inferior potency of nelfinavir compared with ritonavir-boosted PIs, integrase strand transfer inhibitors (INSTIs), and efavirenz make nelfinavir an agent not recommended for children who are initiating therapy.

## 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.<sup>11,12</sup> 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.<sup>13,14</sup> In a study 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 a viral load of <400 copies/mL at 48 weeks of treatment.<sup>15</sup> 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 infection 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.<sup>16</sup>

## 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 INST plus NRTI plus PI/NNRTI). Although studies containing three classes of drugs have demonstrated these regimens to be safe and effective in previously treated HIV-infected 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.<sup>17-21</sup> Ongoing studies, however, are investigating three drug classes as treatment in HIV-infected 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.<sup>22</sup> There has been speculation that poor tolerance and 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 a standard NNRTI-based three-drug regimen versus a four-drug regimen (three NRTIs and an NNRTI). After a 36-week induction period, the children on the 4-drug regimen were continued on a dual NRTI plus NNRTI or an all NRTI-based regimen. Although early benefits in CD4 T lymphocyte improvement and virologic control were observed in the four-drug arm, these benefits were not sustained after de-intensification to the three-NRTI arm.<sup>23</sup> Furthermore, after a median of 3.7 years on therapy, children in the initial 4-drug arm who changed to an all NRTI-based regimen had significantly poorer virologic control.<sup>24</sup> 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.

### **Ritonavir-Boosted Saquinavir**

A saquinavir/ritonavir-based regimen compared with a LPV/r-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naïve adults.<sup>25</sup> 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.

### **Stavudine-Containing Regimens**

**Stavudine-containing regimens, including the dual-NRTI combination of stavudine/didanosine, are not recommended for use as initial therapy because of greater toxicity compared to other available NRTI combinations.** In pediatric studies, stavudine-containing regimens demonstrated virologic efficacy and were well tolerated.<sup>26-29</sup> However, in studies in adults, stavudine with and without didanosine was associated with greater toxicity.<sup>30,31</sup> In addition, **the combination of stavudine/didanosine has been linked with** cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis in women receiving this combination during pregnancy.<sup>32,33</sup>

### **Tipranavir-Based Regimens**

This agent has been studied in treatment-experienced children and adults. Tipranavir is a PI licensed for use in children aged  $\geq 2$  years. Tipranavir-based regimens are not recommended because higher doses of ritonavir to boost tipranavir must be used 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***

A number of ARV drugs and drug regimens are not recommended for initial therapy in ARV-naïve 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 pharmacokinetic (PK) and safety data to recommend their use as components of an initial therapeutic regimen in children. These agents include maraviroc (CCR5 antagonist), elvitegravir (INSTI), and etravirine (NNRTI). 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 be considered as recommended agents or regimens. These are summarized below and also listed in [Table 9](#).

### **Darunavir with Low-Dose Ritonavir When Administered Once Daily (for Children Aged $\geq 3$ 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 now FDA-approved, the Panel is concerned about the lack of efficacy data for individuals aged  $\geq 3$  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  $\geq 3$  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 enhance ease of use and support adherence if no darunavir-associated resistance mutations are present.

### **Efavirenz for Children Aged $\geq 3$ Months to 3 Years**

Efavirenz is FDA-approved for use in children as young as 3 months who weigh at least 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 younger than 3 years at this time (see [Efavirenz](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)). Based on the recommended efavirenz dosage for children younger than 3 years, the IMPAACT P1070 study estimated the variability in area under the curve (AUC) for efavirenz based on polymorphisms in cytochrome P (CYP) 2B6 516. The findings suggest that 38% of extensive metabolizers would have sub-therapeutic AUCs and 67% of poor metabolizers would have excessive AUCs based on recommended dosing.<sup>34</sup> Thus, should efavirenz be considered, CYP2B6 genotyping that predicts efavirenz metabolic rate should be performed, if available. Therapeutic drug monitoring can also be considered.

## Elvitegravir-Based Regimens

Elvitegravir is an INSTI available as a tablet and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TDF (Stribild) and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) (Genvoya). All are FDA-approved for use as ART in HIV-1-infected ART-naive adults. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide is FDA-approved for use in ART-naive children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg.

Elvitegravir tablets must be taken in combination with a low-dose ritonavir-boosted PI. A small study (14 participants) of Stribild in treatment-naive children and adolescents aged 12 to 17 years has reported PK, tolerability, and virologic efficacy at 24 weeks. The therapy was well tolerated, steady state exposure was similar to adults and, at 24 weeks, all subjects had viral loads  $< 400$  copies/mL and 11 had viral loads  $< 50$  copies/mL. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide was studied in 49 ART-naive children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg and demonstrated PK parameters similar to those for the combination in adults, was well tolerated and, at week 24, all subjects had viral loads  $< 50$  copies/mL.<sup>35</sup> Tablets containing elvitegravir/cobicistat/emtricitabine/TAF are recommended as “preferred” for children aged  $\geq 12$  years and weighing  $\geq 35$  kg. Tablets containing elvitegravir/cobicistat/emtricitabine/TDF are recommended only for adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg and in sexual maturity stage 4 or 5 (see [What to Start](#)). However, data are insufficient to recommend elvitegravir as part of an initial regimen for children aged  $< 12$  years.

## Etravirine-Based Regimens

Etravirine is an NNRTI that has been studied in treatment-experienced children aged  $\geq 6$  years.<sup>36,37</sup> 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 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 dosage. Dose adjustments were required in patients not receiving a potent CYP450 3A4 inhibitor or inducer.<sup>38</sup> 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-drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

**Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children** (page 1 of 2)

Regimen or ARV Component	Rationale for Being Not Recommended
Unboosted <b>ATV</b> -containing regimens in children	Reduced exposure
<b>DRV</b> -based regimens once daily in children $\geq 3$ to 12 years	Insufficient data to recommend
Unboosted <b>DRV</b>	Use without ritonavir has not been studied.
Dual (full-dose) PI regimens	Insufficient data to recommend Potential for added toxicities
Dual NRTI combination of <b>ABC plus ddl</b>	Insufficient data to recommend
Dual NRTI combination of <b>ABC plus TDF</b>	Insufficient data to recommend

**Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children** (page 2 of 2)

Regimen or ARV Component	Rationale for Being Not Recommended
Regimens containing d4T	Increased toxicities
Dual NRTI combination of TDF plus ddI	Increase in concentrations; high rate of virologic failure
EFV-based regimens for children aged <3 years	Appropriate dose not determined
T20-containing regimens	Insufficient data to recommend Injectable preparation
ETR-based regimens	Insufficient data to recommend
EVG-based regimens	Insufficient data to recommend regimens containing EVG 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 <a href="#">What to Start</a> )
FPV-based regimens	Reduced exposure Medication burden
IDV-based regimens	Renal toxicities
LPV/r dosed once daily	Reduced drug exposure
MVC-based regimens	Insufficient data to recommend
NFV-based regimens	Variable PK Appropriate dose not determined in young infants
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Insufficient data to recommend
Full-dose RTV or use of RTV as the sole PI	GI intolerance Metabolic toxicity
Regimens containing three NRTIs and an NNRTI	Added cost and complexity outweighs any benefit
SQV-based regimens	Limited dosing and outcome data
TDF-containing regimens in children aged <2 years	Potential bone toxicity Appropriate dose has yet to be determined.
TPV-based regimens	Increased dose of RTV for boosting Reported cases of intracranial hemorrhage

**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; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

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

<b>ART Regimens <u>Never</u> Recommended for Children</b>		
<b>Regimen</b>	<b>Rationale</b>	<b>Exceptions</b>
<b>One ARV drug alone (monotherapy)</b>	<ul style="list-style-type: none"> <li>• Rapid development of resistance</li> <li>• Inferior antiviral activity compared with combination including <math>\geq 3</math> ARV drugs</li> <li>• Monotherapy “holding” regimens associated with more rapid CD4 decline compared to non-suppressive ART</li> </ul>	<ul style="list-style-type: none"> <li>• HIV-exposed infants (with negative viral testing) during 6-week period of prophylaxis to prevent perinatal transmission of HIV</li> </ul>
<b>Two NRTIs Alone</b>	<ul style="list-style-type: none"> <li>• Rapid development of resistance</li> <li>• Inferior antiviral activity compared with combination including <math>\geq 3</math> ARV drugs</li> </ul>	<ul style="list-style-type: none"> <li>• Not recommended for initial therapy</li> <li>• For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.</li> </ul>
<b>TDF <u>plus</u> ABC <u>plus</u> (3TC <u>or</u> FTC) as a Triple-NRTI Regimen</b>	<ul style="list-style-type: none"> <li>• High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults.</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>TDF <u>plus</u> ddl <u>plus</u> (3TC <u>or</u> FTC) as a Triple-NRTI Regimen</b>	<ul style="list-style-type: none"> <li>• High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults.</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>ARV Components <u>Never</u> Recommended as Part of an ARV Regimen for Children</b>		
<b>Regimen</b>	<b>Rationale</b>	<b>Exceptions</b>
<b>ATV <u>plus</u> IDV</b>	<ul style="list-style-type: none"> <li>• Potential additive hyperbilirubinemia</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>Dual-NNRTI Combinations</b>	<ul style="list-style-type: none"> <li>• Enhanced toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<u>Dual-NRTI Combinations:</u>	<ul style="list-style-type: none"> <li>• Similar resistance profile and no additive benefit</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
• <b>3TC <u>plus</u> FTC</b>		
• <b>d4T <u>plus</u> ZDV</b>	<ul style="list-style-type: none"> <li>• Antagonistic effect on HIV</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>EFV for Sexually Active Adolescent Girls of Childbearing Potential When Reliable Contraception Cannot Be Ensured</b>	<ul style="list-style-type: none"> <li>• Teratogenicity in primates (see <a href="#">General Principles Regarding Use of Antiretroviral Drugs during Pregnancy Teratogenicity</a>)</li> </ul>	<ul style="list-style-type: none"> <li>• When no other ARV option is available and potential benefits outweigh risks</li> </ul>
<b>NVP as Initial Therapy in Adolescent Girls with CD4 Count <math>&gt;250</math> cells/mm<sup>3</sup> or Adolescent Boys with CD4 Count <math>&gt;400</math> cells/mm<sup>3</sup></b>	<ul style="list-style-type: none"> <li>• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups</li> </ul>	<ul style="list-style-type: none"> <li>• Only if benefit clearly outweighs risk</li> </ul>
<b>Unboosted SQV, DRV, or TPV</b>	<ul style="list-style-type: none"> <li>• Poor oral bioavailability</li> <li>• Inferior virologic activity compared with other PIs</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; d4T = stavudine; ddl = 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

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