What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated April 27, 2017; last reviewed April 27, 2017)

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 ARV drugs, 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 ≥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 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, 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 ≥2 years.2-5 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. 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. 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. 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 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. 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.

Regimens Containing Three Drug Classes
Data are insufficient to recommend initial regimens containing agents from 3 drug classes (e.g., NRTI plus NNRTI plus PI or INSTI plus NRTI plus PI/NNRTI). Although studies containing 3 classes of drugs have demonstrated these regimens to be 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 3 drug classes, which could severely limit future treatment options. Ongoing studies, however, are investigating 3 drug classes as treatment in neonates.

Regimens Containing Three NRTIs and an NNRTI
Data are currently insufficient to recommend a regimen of 3 NRTIs plus an NNRTI in young infants. A recent review of 9 cohorts from 13 European countries suggested superior responses to this 4-drug regimen when compared to boosted PI or 3-drug NRTI regimens. 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 3-drug regimen versus a 4-drug regimen (3 NRTIs and 1 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 (CD4) improvement and virologic control were observed in the 4-drug arm, these benefits were not sustained after de-intensification to the 3-NNRTI arm. 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. Based on demonstrated benefits of recommended 3-drug regimens and lack of additional efficacy data on the 4-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-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.

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. However, in studies in adults, stavudine with and without didanosine was associated with greater toxicity. 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.

Tipranavir-Based Regimens
This agent has been studied in treatment-experienced children and adults. Tipranavir is a PI licensed for use in children aged ≥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
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. These agents include 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 are also listed in Table 9.

Daranavir with Low-Dose Ritonavir When 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 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 enhance ease of 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 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 aged <3 years at this time (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). Based on the recommended efavirenz dosage for children aged <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 extensivemetabolizers would have sub-therapeutic AUCs and 67% of poor metabolizers would have excessive AUCs based on recommended dosing. 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 for Children Aged <12 Years**

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 ART-naive adults with HIV-1 infection. Elvitegravir/cobicistat/emtricitabine/TAF is FDA-approved for use in ART-naive children and adolescents aged ≥12 years and weighing ≥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; 11 had viral loads <50 copies/mL. Elvitegravir/cobicistat/emtricitabine/TAF was studied in 49 ART-naive children and adolescents aged ≥12 years and weighing ≥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. Tablets containing elvitegravir/cobicistat/emtricitabine/TAF are recommended as “preferred” for children aged ≥12 years and weighing ≥35 kg. Tablets containing elvitegravir/cobicistat/emtricitabine/TDF are recommended only for adolescents aged ≥12 years and weighing ≥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 ≥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 4 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. 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>
<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>
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<tr>
<td></td>
<td>Potential for added toxicities</td>
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<tr>
<td>Dual NRTI combination of <strong>ABC plus ddI</strong></td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Dual NRTI combination of <strong>ABC plus 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 plus 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>
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<tr>
<td></td>
<td>Injectable preparation</td>
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<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>Potential for added toxicities</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><strong>Full-dose RTV</strong> or use of <strong>RTV</strong> as the sole PI</td>
<td>GI intolerance</td>
</tr>
<tr>
<td></td>
<td>Metabolic toxicity</td>
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<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 RTV for boosting</td>
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<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
### ART Regimens Never Recommended for Children

<table>
<thead>
<tr>
<th>Regimen</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 ddl 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>
</tbody>
</table>
| Dual-NRTI Combinations:  
• 3TC plus FTC  
• d4T plus ZDV | • Similar resistance profile and no additive benefit  
• Antagonistic effect on HIV | • No exceptions  
• No exceptions |
| NVP as Initial Therapy in Adolescent Girls with CD4 Count >250 cells/mm³ or Adolescent Boys with CD4 Count >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 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

### References


Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection


