What Not to Start: Regimens Not Recommended for Use in Antiretroviral-Naive Children

Updated: April 11, 2023
Reviewed: April 11, 2023

This section describes antiretroviral (ARV) drugs and drug combinations that either are not recommended for use in ARV-naive children or lack sufficient data to recommend their use in ARV-naive children. Although many ARV agents and combinations are available, some are not recommended for use as part of an initial regimen in ARV-naive children, but they may be used in ARV-experienced children (see Recognizing and Managing Antiretroviral Treatment Failure). Several ARV drugs that are no longer available or recommended for use in children for several years have been removed from this chapter, including the nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and didanosine; the protease inhibitors (PIs) indinavir, nelfinavir, saquinavir, tipranavir (TPV), and fosamprenavir; and the fusion inhibitor enfuvirtide (see Archived Drugs in Appendix A: Pediatric Antiretroviral Drug Information). The PI ritonavir is no longer recommended for use as the sole PI in an ARV regimen but is used at a reduced dose as a pharmacokinetic (PK) enhancer (boosting agent) with other ARV drugs (e.g., atazanavir, darunavir).

The Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) classifies ARV drugs and drug combinations that are not recommended for use in ARV-naive children into one of three categories:

- *Not Recommended for Initial Therapy:* These include ARV drugs and drug combinations that are not recommended for initial therapy in ARV-naive children because they produce an inferior virologic response, they pose potential serious safety concerns (including potentially overlapping toxicities), they are associated with pharmacologic antagonism, or better options are available within a drug class. These drugs and drug combinations are listed in Table 10, and selected drugs or drug combinations are discussed below.
- *Insufficient Data to Recommend for Initial Therapy:* ARV drugs and drug combinations that are approved for use in adults but have insufficient, limited, or no PK and/or safety data for children cannot be recommended for 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 also are listed in Table 10, and selected drugs or drug combinations are discussed below.
- *Antiretroviral Drug Regimens That Are Never Recommended:* Several ARV drug and drug combinations should never be used in children or adults. They are summarized in Table 11. Clinicians also should be aware of the components of fixed-dose combination (FDC) tablets so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Antiretroviral Drugs and Drug Combinations Not Recommended for Initial Therapy in Children

Atazanavir Without Ritonavir or Cobicistat Boosting

Although unboosted atazanavir (ATV) is approved by the U.S. Food and Drug Administration (FDA) for use in treatment-naive adolescents—aged ≥13 years and weighing ≥40 kg—who are unable to

tolerate ritonavir (RTV), data from the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)/Pediatric AIDS Clinical Trials Group (PACTG) 1020A study indicate that adolescents require higher doses of unboosted ATV (as measured by milligram per meter squared of body surface area) than adults to achieve adequate drug concentrations.[1] Because of these findings, the Panel **does not recommend** using ATV without RTV boosting.

Efavirenz-Based Regimens for Children Aged ≥3 Months to 3 Years

Efavirenz (EFV) is approved by the FDA for use in children aged >3 months and weighing ≥3.5 kg. An EFV-based regimen was shown to have variable PKs in studies of young children; therefore, at this time the Panel does not recommend using EFV in children aged <3 years (see the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information). When the use of EFV is being considered for children aged <3 years, cytochrome P450 (CYP) 2B6 genotyping should be performed, if available, to predict a patient's metabolic rate for EFV. Therapeutic drug monitoring also can be considered. Additionally, EFV in children <3 years may be considered in the setting of HIV/tuberculosis coinfection, because EFV is one of the few ARVs with minimal drug–drug interactions seen with other ARVs and rifampin.[2]

Etravirine-Based Regimens

Etravirine (ETR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that has been studied in treatment-experienced children aged ≥1 years and now is approved by the FDA for use in children aged ≥2 years and weighing ≥10 kg.[3-5] ETR is associated with multiple interactions with other ARV drugs, including TPV/ritonavir, ATV/ritonavir, and unboosted PIs, and must be administered twice daily. The use of ETR likely will not be studied in treatment-naive children.

Maraviroc-Based Regimens

Maraviroc (MVC) is an entry inhibitor approved by the FDA for use in children weighing ≥2 kg who have CCR5-tropic HIV-1. It has been used infrequently in children. A recent dose-finding study administered both the liquid and tablet formulations of MVC to treatment-experienced children aged 2 to 18 years who were grouped into four age cohorts.[6] The initial dose was based on body surface area and scaled from the recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP3A4 inhibitor or inducer.[6] A recent study of MVC in newborns at risk of HIV acquisition and weighing at least 2 kg established a dosing protocol that achieved target exposures and was deemed safe. No apparent differences in PK parameters were observed among infants of mothers with exposure to EFV and those without. None of the infants had HIV infection, nor were they receiving potent CYP3A inhibitors.[7] As an entry inhibitor, MVC is under study in intensive treatment trials because of its hypothetical potential to limit the establishment of cell-associated viral reservoirs. However, MVC has several features that limit its role for routine uses, including multiple drug interactions, the need to be administered twice daily, and the fact that tropism assays must be performed prior to its use to ensure the presence of only CCR5-tropic virus. For those reasons, MVC **is not recommended** by the Panel for first-line treatment in neonates or older children.

Cabotegravir With or Without Rilpivirine for Oral or Intramuscular Injections

In 2021, the FDA approved long-acting injectable formulations of cabotegravir (CAB), a novel INSTI, and the NNRTI rilpivirine (RPV) for the treatment of HIV infection in adults to replace a current, stable ARV regimen in patients with no prior history of treatment failure and no known or suspected resistance to CAB or RPV who have demonstrated sustained viral suppression

(e.g., 3–6 months). These two long-acting injectable ARVs are co-packaged and marketed as Cabenuva. In March 2022, the FDA approved Cabenuva for use in children and adolescents aged ≥12 years and weighing ≥35 kg. An oral lead-in with the oral formulations of the ARVs for at least 28 days is recommended to assess tolerability. The long-acting injectable formulations can then be administered on a monthly or an every 2-month schedule. Clinical trials in adolescents are ongoing and planned for younger children. The regimen of LAI CAB and RPV **is not approved or recommended** for initial ARV therapy.

Regimens That Contain Only Nucleoside Reverse Transcriptase Inhibitors

In adult trials, regimens that contain only NRTIs have shown less potent virologic activity than NNRTI–based or PI-based regimens.[8,9] Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited to small observational studies.[10,11] In a study on the use of the triple-NRTI regimen abacavir plus lamivudine (3TC) plus zidovudine in ARV-experienced children, this combination showed evidence of only modest viral suppression; only 10 of the 102 children had viral loads of <400 copies/mL at Week 48 of treatment.[12] Therefore, regimens that contain only NRTIs **are not recommended** for treatment-naive or treatment-experienced children.

Regimens That Contain Three Drug Classes

The Panel **does not recommend** using regimens that contain agents from three drug classes as initial regimens (e.g., an NRTI plus an NNRTI plus a PI or an integrase strand transfer inhibitor plus an NRTI plus a PI or NNRTI). Although studies of regimens that contain three classes of drugs have demonstrated that these regimens are safe and effective in ARV-experienced children and adolescents, these regimens have not been studied as initial regimens in treatment-naive children and adolescents. These regimens also have the potential to induce resistance to three drug classes, which could severely limit future treatment options.[13-17] Ongoing studies are investigating the use of drugs from three drug classes to treat neonates.

Regimens That Contain Three Nucleoside Reverse Transcriptase Inhibitors and a Non-Nucleoside Reverse Transcriptase Inhibitor

Current data are insufficient to recommend using a regimen that contains three NRTIs plus an NNRTI in young infants. A review of nine cohorts from 13 European countries suggested that this four-drug regimen produced responses that were superior to the responses observed in patients receiving boosted-PI regimens or three-drug NRTI regimens.[18] There has been speculation that poor tolerance and poor adherence to a PI-based regimen may account for some of the differences. The AntiRetroviral Research for Watoto (ARROW) trial, conducted in Uganda and Zimbabwe, randomized 1,206 children (with a median age of 6 years) to receive either a standard NNRTI-based, three-drug regimen (two NRTIs and one NNRTI) 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 regimen that contained two NRTIs plus one NNRTI or a three-NRTI regimen. Although improvements in CD4 T lymphocyte (CD4) cell counts were observed at Week 36 (with a percentage change of approximately 14.4% in the four-drug arm compared with 12.6% in the three-drug arm), these benefits were not sustained after patients switched to the three-drug regimens for the duration of the study. Furthermore, no differences in viral suppression rates were observed between the two arms at Week 36.[19] Because three-drug regimens have been shown to be effective and well tolerated and because efficacy data are lacking for the four-drug regimen, the Panel **currently does not recommend** the four-drug regimen.

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

Several ARV drugs and drug regimens are not recommended for use as initial therapy in ARV-naive children or for specific age groups because of insufficient pediatric data. In some cases, new agents have shown promise in adult clinical trials 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 because of insufficient data. As new data become available, these agents may become recommended agents or regimens, as summarized below and listed in Table 10.

Darunavir With Low-Dose Ritonavir-Based Regimens Administered Once Daily for Children Aged ≥3 Years to <12 Years

Whereas modeling studies identified a once-daily dosing schedule for darunavir/ritonavir (DRV/r) that is now approved by the FDA, the Panel is concerned about the lack of direct PK studies for this approach in individuals aged ≥3 years to <12 years. Therefore, the data are not sufficient to recommend once-daily dosing for initial therapy in this age group. For children aged ≥3 years to <12 years, twice-daily DRV/r is a *Preferred* drug combination. For older children who have undetectable viral loads while receiving a twice-daily DRV/r-based regimen, practitioners can consider switching to once-daily DRV/r dosing if no DRV-associated resistance mutations are present. Once-daily dosing helps support adherence by making this drug combination easier to use.

Fostemsavir-Containing Regimens

Fostemsavir (FTR) is an HIV-1 glycoprotein (gp120)-directed attachment inhibitor that is not approved for use in pediatric patients. FTR was approved by the FDA in 2020 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are failing their current ART regimen due to resistance, intolerance, or safety considerations. A PK and safety study of FTR in children and adolescents ≥20 kg (PENTA Foundation: NCT04648280) will soon be open to enrollment. At this time, the Panel **does not recommend** FTR as part of an initial treatment regimen for HIV-1 infection in children.

Ibalizumab-Containing Regimens

Ibalizumab (IBA) is a humanized IgG4 monoclonal antibody that binds to CD4 extracellular domain 2 and prevents conformational changes in the CD4-HIV envelope gp120 essential for viral entry, thereby blocking HIV entry into CD4 cells.[20] It was approved for use in adults with HIV-1 infection who are heavily pretreated, have multidrug-resistant virus, and are experiencing treatment failure. IBA has an orphan drug designation exempting the requirement for pediatric studies under the Pediatric Research Equity Act. At this time, because there is no experience with IBA in children, the Panel **does not recommend** its use as initial treatment for HIV-1 infection.

Two-Drug Regimens

In adults, oral two-drug/two-class ARV regimens can be used in patients who have achieved and sustained viral suppression on a three-drug ART regimen and may be used for initial therapy in some individuals. In general, adults who have had viral suppression for at least 3 to 6 months and with

known susceptibility to the ARVs in the two-drug regimen have success after switching to these regimens. Regimens that demonstrated efficacy in adult clinical trials include dolutegravir (DTG) plus RPV, DTG plus 3TC or emtricitabine (FTC), and boosted DRV plus DTG. At this time, no data support this strategy in children, and it **is not recommended** by the Panel. Although the Panel **does not recommend** oral two-drug regimens for initial treatment in children, some two-drug regimens might be considered for adolescents receiving ART when simplification or avoidance of NRTIs is desired based on data from adults, see Modifying Antiretroviral Regimens in Children With Sustained Virologic Suppression on Antiretroviral Therapy.

A two-drug/two-class regimen of LAI CAB and RPV has been approved by the FDA for use in adults and in children and adolescents aged ≥12 years and weighing ≥35 kg who have achieved and sustained viral suppression on another combination ARV regimen. However, this LAI regimen **is not recommended** for initial therapy.

Table 10. Antiretroviral Regimens or Components That Are Not Recommended for Initial Treatment of HIV Infection in Children and Adolescents

ARV Regimen	Rationale
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Potential to induce multiclass resistance Use as an initial regimen in children has not been studied
Regimens containing three NRTIs and one NNRTI	Added cost and complexity outweighs any benefit
Full-dose, dual-PI regimens	Insufficient data to recommend; potential for added toxicities
Oral regimens containing only two ARVs	Not FDA approved for pediatric use
ARV Component	**Rationale**
Unboosted ATV-containing regimens in children	Inadequate drug exposure
CAB	Not FDA approved for use in ARV-naive individuals or in children aged <12 years and weighing <35 kg
DRV/r in children <3 years	Potential for seizures
Once-daily DRV-based regimens in children aged ≥3 years to <12 years	Insufficient data to recommend
EFV-based regimens for children aged <3 years	CYP2B6 genotyping required to determine appropriate dosing
ETR-based regimens	Insufficient data to recommend; unlikely to be used as initial therapy
FTR	Not FDA approved for use in ARV-naive adults or for pediatric use
IBA	Not FDA approved for use in ARV-naive adults or for pediatric use
LPV/r dosed once daily	Inadequate drug exposure
MVC-based regimens	Only effective for CCR5-tropic virus
TDF-containing regimens in children aged <2 years	Potential bone toxicity Appropriate dose has yet to be determined

Key: ARV = antiretroviral; ATV = atazanavir; CAB = cabotegravir; DRV = darunavir; DRV/r = darunavir/ritonavir; FDA = U.S. Food and Drug Administration; EFV = efavirenz; ETR = etravirine; FTR = fostemsavir; GI = gastrointestinal; IBA = ibalizumab; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

Table 11. Antiretroviral Regimens or Components That Are Never Recommended for Treating HIV in Children and Adolescents[a]

ARV Regimen or Component	Rationale	Exceptions
One ARV Drug Alone (Monotherapy)	Rapid development of resistance Inferior antiviral activity compared with regimens that include ≥3 ARV drugs Monotherapy "holding" regimens are associated with more rapid CD4 count declines than nonsuppressive ART.	Infants with perinatal HIV exposure and negative virologic tests who are receiving 4–6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	Rapid development of resistance Inferior antiviral activity compared with regimens that include ≥3 ARV drugs	Not recommended for initial therapy Some clinicians may opt to continue using two NRTIs alone in patients who achieve virologic goals with this regimen.
Any Regimen Containing Both 3TC Plus FTC	Similar resistance profile and no additive benefit	No exceptions
Any Regimen Containing Both TDF and TAF	No data to support potential additive efficacy or toxicity	No exceptions
Dual-NNRTI Combinations	Enhanced toxicity	No exceptions
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
NVP as Component of Initial ARV Therapy Regimen in Adolescent Girls With CD4 Counts >250 cells/mm^3 or Adolescent Boys With CD4 Counts >400 cells/mm^3	Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	Only if benefit clearly outweighs risk

[a] Several ARV drugs that are no longer available or that have not been recommended for use in children for several years have been removed from this chapter, including the NRTIs stavudine and didanosine; the protease inhibitors fosamprenavir indinavir, nelfinavir, saquinavir, and tipranavir; and the fusion inhibitor enfuvirtide (see Archived Drugs).

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

References

1. Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-1496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21610486.

2. Bwakura Dangarembizi M, Samson P, Capparelli EV, et al. Establishing dosing recommendations for efavirenz in HIV/TB-coinfected children younger than 3 years. *J Acquir Immune Defic Syndr*. 2019;81(4):473-480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31241542.

3. Konigs C, Feiterna-Sperling C, Esposito S, et al. Pharmacokinetics and short-term safety and tolerability of etravirine in treatment-experienced HIV-1-infected children and adolescents. *AIDS*. 2012;26(4):447-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22156961.

4. Tudor-Williams G, Cahn P, Chokephaibulkit K, et al. Etravirine in treatment-experienced, HIV-1-infected children and adolescents: 48-week safety, efficacy and resistance analysis of the phase II PIANO study. *HIV Med*. 2014;15(9):513-524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24589294.

5. MacBrayne CE, Rutstein RM, Wiznia AA, et al. Etravirine in treatment-experienced HIV-1-infected children 1 year to less than 6 years of age. *AIDS*. 2021;35(9):1413-1421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33831904.

6. Giaquinto C, Mawela MP, Chokephaibulkit K, et al. Pharmacokinetics, safety and efficacy of maraviroc in treatment-experienced pediatric patients infected with CCR5-tropic HIV-1. *Pediatr Infect Dis J*. 2018;37(5):459-465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29023357.

7. Rosebush JC, Best BM, Chadwick EG, et al. Pharmacokinetics and safety of maraviroc in neonates. *AIDS*. 2021;35(3):419-427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33252481.

8. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS*. 2003;17(14):2045-2052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14502007.

9. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*. 2003;17(7):987-999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12700448.

10. Saavedra J, Mccoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. Presented at: 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001. Chicago, IL.

11. Handforth J, Sharland M. Triple nucleoside reverse transcriptase inhibitor therapy in children. *Paediatr Drugs*. 2004;6(3):147-159. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15170362.

12. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*. 2001;107(1):E4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11134468.

13. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. 2000;182(6):1769-1773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11069252.

14. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-1881. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10601506.

15. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(7):659-663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12237599.

16. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(12):1113-1121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10954886.

17. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11880966.

18. Judd A, and EP, Paediatric HIV Cohort Collaboration study group in EuroCoord. Early antiretroviral therapy in HIV-1-infected infants, 1996–2008: treatment response and duration of first-line regimens. *AIDS*. 2011;25(18):2279-2287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21971357.

19. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23473847.

20. Moore JP, Sattentau QJ, Klasse PJ, Burkly LC. A monoclonal antibody to CD4 domain 2 blocks soluble CD4-induced conformational changes in the envelope glycoproteins of

human immunodeficiency virus type 1 (HIV-1) and HIV-1 infection of CD4+ cells. *J Virol*. 1992;66(8):4784-4793. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1378510.