



Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated September 12, 2019; last reviewed September 12, 2019)

Panel's Recommendations

- The selection of an initial regimen should be individualized based on several factors, including the characteristics of the proposed regimen, the patient's characteristics, drug efficacy, potential adverse effects, patient and family preferences, and the results of viral resistance testing (**AIII**).
- For treatment-naive children, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends initiating antiretroviral therapy with three drugs: a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone plus an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor (**AI***).
- Table 7 provides a list of Panel-recommended regimens that are designated as *Preferred* or *Alternative*; recommendations vary by a patient's age, weight, and sexual maturity rating.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

[†] Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Criteria Used for Recommendations

In general, the recommendations of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) are based on reviews of pediatric and adult clinical trial data published in peer-reviewed journals, data prepared by manufacturers for Food and Drug Administration (FDA) review, and data presented in abstract format at major scientific meetings. Few randomized, Phase 3 clinical trials of antiretroviral therapy (ART) in pediatric patients have directly compared different treatment regimens. Most pediatric drug data come from Phase 1/2 safety and pharmacokinetic (PK) trials and nonrandomized, open-label studies. In general, even in studies of adults, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 T lymphocyte (CD4) cell count and HIV RNA levels. The Panel continually modifies recommendations on optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities are recognized.

When developing recommendations for specific drugs or regimens, the Panel considers the following information:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with a specific drug or regimen;
- Incidence and types of short-term and long-term drug toxicity in people who are taking the regimen, focusing on toxicities that are reported in children;
- Availability and acceptability of formulations that are appropriate for pediatric use, including palatability, ease of preparation (e.g., syrups vs. powders), pill size, and the number of pills or volume of oral solution needed for an appropriate dose;
- Dosing frequency and food and fluid requirements; *and*
- Potential for drug interactions with other medications.

The Panel classifies recommended drugs or drug combinations into one of two categories:

- *Preferred*: Drugs or drug combinations are designated as *Preferred* for use in treatment-naïve children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies using surrogate markers have demonstrated safety and efficacy. Additional considerations are listed above.
- *Alternative*: Drugs or drug combinations are designated as *Alternative* for initial therapy when clinical trial data in children or adults show efficacy, but the drugs and drug combinations have disadvantages when compared with *Preferred* regimens. These disadvantages include: more limited experience with use of the drugs or regimen in children than in adults; the extent of antiviral efficacy or durability is less well defined in children, or the drug or regimen is less effective or durable than a *Preferred* regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.

Factors to Consider When Selecting an Initial Regimen

An ART regimen for children should generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an active drug from one of the following classes: integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Choice of a regimen should be individualized based on several factors, including the characteristics of the proposed regimen; the patient's age, weight, sexual maturity rating (SMR), and other characteristics; and the results of viral resistance testing. Drug recommendations often include both age and weight limitations. Although age can be used as a rough guide, body weight (when available) is the preferred determinant for selecting a specific drug. An exception to this guide is for infants who are less than 14 days of age. Many drugs that are recommended for use in very young infants do not have dosing recommendations for premature infants. Additional information regarding dosing recommendations in this population can be found in [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#). The advantages and disadvantages of each regimen are described in detail in the sections that follow and in Table 8. Additional information regarding the advantages and disadvantages of specific drug combinations can be found in the [What to Start](#) section of the [Adult and Adolescent Antiretroviral Guidelines](#). Specific information about the clinical efficacy, adverse events (AEs), and dosing recommendations for each drug can be found in [Appendix A: Pediatric Antiretroviral Drug Information](#). In addition, because ART will most likely need to be administered throughout the patient's life, clinicians should consider potential barriers to adherence. These barriers may include complex dosing schedules, food requirements, the need to use multiple formulations to achieve an appropriate dose, palatability problems, and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after the patient has been assessed and the clinician has counseled the patient and caregivers about adherence to therapy.

Emtricitabine, lamivudine, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have antiviral activity and efficacy against hepatitis B virus (HBV) and should be considered for use in children with HBV/HIV coinfection. For a comprehensive [review of this topic](#), as well as a review of [hepatitis C](#) and [tuberculosis](#) in patients with HIV, see the [Pediatric Opportunistic Infection Guidelines](#).

Choosing an Initial Antiretroviral Regimen for Children with HIV

Preferred regimens for initial therapy include INSTI-based, NNRTI-based, or boosted PI-based regimens. A regimen should be chosen after considering the patient's individual characteristics (especially age), the results of viral drug resistance testing, drug efficacy, potential AEs, pill size, and dosing frequency. Adherence to a prescribed regimen is necessary; therefore, the preferences of the patient and caregivers should also be considered when choosing a regimen.

Clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a

PI-based regimen for initial therapy. Three pediatric studies have compared an NNRTI-based regimen to a PI-based regimen, and results varied based on the age of the population studied and the specific drug used within the class.

- The P1060 study demonstrated the superiority of a lopinavir/ritonavir (LPV/r)-based regimen over a nevirapine-based regimen in infants and children aged 2 months to 35 months, regardless of maternal or infant exposure to peripartum, single-dose nevirapine prophylaxis. In children with prior nevirapine exposure, 21.7% of children receiving the LPV/r-based regimen experienced death, virologic failure, or toxicity by Week 24 compared to 39.6% of children receiving the nevirapine-based regimen. For children with no prior nevirapine exposure, death, virologic failure, and toxicity occurred in 18.4% of children receiving the LPV/r-based regimen and 40.1% of children receiving the nevirapine-based regimen.¹
- Those in the nevirapine group demonstrated greater, but not statistically significant, improvements in CD4 counts and growth parameters. However, improvements in CD4 cell counts were only maintained up to 1 year after initiation of ART.² Similar improved immune and growth parameters were also reported in the NEVEREST study, where these parameters were compared in children who switched to a nevirapine-containing regimen and those who continued on a LPV/r-containing regimen after achieving virologic suppression.³ Improvements in metabolic parameters have also been seen in children who switched from LPV/r to efavirenz at or after 3 years of age.⁴
- PENPACT-1 (PENTA 9/PACTG 390) compared a PI-based regimen and a NNRTI-based regimen in treatment-naïve children aged 30 days to <18 years (the study did not dictate the specific NNRTI or PI). In the PI-based regimen group, 49% of children received LPV/r and 48% received nelfinavir; in the NNRTI-based regimen group, 61% of children received efavirenz and 38% received nevirapine. After 4 years of follow-up, 73% of children who were randomized to receive PI-based therapy and 70% who were randomized to receive NNRTI-based therapy remained on their initial ART regimen. In both groups, 82% of children had viral loads <400 copies/mL.⁵
- The PROMOTE-pediatrics trial demonstrated comparable virologic efficacy among children who were randomized to receive either an NNRTI-based or a LPV/r-based ART regimen.⁶ Children were aged 2 months to <6 years and had no perinatal exposure to nevirapine. Selection of the NNRTI was based on age (children aged <3 years received nevirapine, and those aged >3 years primarily received efavirenz). The proportion of children with HIV RNA levels <400 copies/mL at 48 weeks was 80% in the LPV/r arm versus 76% in the NNRTI arm, a difference of 4% that was not statistically significant (95% confidence interval [CI], -9% to +17%).

Clinical investigation of INSTI-based regimens in children has been limited to noncomparative studies that have evaluated the safety, tolerability, and PKs of these drugs. The recommendation for using an INSTI as part of an initial regimen is based largely on extrapolation from adult comparative trials that showed that INSTI-containing regimens have superior efficacy when compared to PI-containing and NNRTI-containing regimens^{7,8} and small studies in ART-naïve adolescents.⁹

When combined with two NRTIs, the following drugs and drug combinations are considered *Preferred* regimens for children:

- Children aged <14 days: Nevirapine
- Children aged <14 days and weighing ≥ 2 kg: Raltegravir
- Children aged ≥ 14 days to <3 years: LPV/r or raltegravir
- Children aged ≥ 3 years and
 - Weighing <25 kg: Atazanavir, atazanavir/ritonavir (ATV/r), twice-daily darunavir/ritonavir (DRV/r), or raltegravir
 - Weighing ≥ 25 kg: Dolutegravir
 - Weighing ≥ 25 kg: Elvitegravir/cobicistat (only the fixed-dose combination [FDC] elvitegravir/cobicistat/emtricitabine/TAF is recommended at this time)

- Adolescents aged ≥ 12 years and weighing ≥ 25 kg: Bictegravir (as the FDC bictegravir/emtricitabine/TAF)

Alternative regimens are shown in Table 7 below.

Integrase Strand Transfer Inhibitor-Based Regimens

Four INSTIs—bictegravir, dolutegravir, elvitegravir, and raltegravir—are approved by the FDA for treating antiretroviral (ARV)-naive adults and children with HIV. These agents have quickly become the recommended regimens in adults because of their virologic efficacy, lack of drug interactions, and favorable toxicity profile. Raltegravir is approved for the treatment of infants and children from birth onwards with weights ≥ 2 kg. Dolutegravir is approved by the FDA for use in children weighing ≥ 30 kg. The FDC bictegravir/emtricitabine/TAF (Biktarvy) is now approved by the FDA for use in children weighing ≥ 25 kg. Elvitegravir has been studied in adolescents in two FDC regimens and in combination with two NRTIs and ritonavir boosting. Bictegravir and dolutegravir, the second-generation INSTIs, have higher barriers to resistance than the first-generation INSTIs raltegravir and elvitegravir^{10,11} and may have more activity against non-B subtypes of HIV.^{12,13}

Table 8 lists the advantages and disadvantages of using INSTIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.

Bictegravir

Bictegravir is available only as part of an FDC tablet that contains bictegravir 50 mg/emtricitabine 200 mg/TAF 25 mg and is marketed as Biktarvy. Bictegravir/emtricitabine/TAF was approved by the FDA in 2018 for use in adults and in 2019 for use in children or adolescents weighing ≥ 25 kg. Biktarvy is approved for use in patients who have no ARV treatment history, and it can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA < 50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of the FDC.

Biktarvy was administered to adolescents aged 12 years to < 18 years and weighing ≥ 35 kg who had maintained viral loads < 50 copies/mL for ≥ 6 months. The drug was well tolerated; all 24 participants in the study had viral loads < 50 copies/mL at Week 24, and drug exposure in these adolescent patients was similar to the exposure observed in adults. Another study demonstrated the efficacy and tolerability of Biktarvy in children aged 6 years to < 12 years who weighed ≥ 25 kg, although serum trough concentrations were more variable in this child cohort than in adolescent or adult cohorts.^{14,15}

The two studies described above were combined and continued for 48 weeks, at which time 74 of 75 participants had viral loads < 50 copies/mL.¹⁴

Recommendation:

- Bictegravir/emtricitabine/TAF is recommended as a Preferred INSTI-based regimen for adolescents aged ≥ 12 years and weighing ≥ 25 kg (AI*) and as an Alternative INSTI-based regimen for children aged ≥ 6 years and weighing ≥ 25 kg (AI*). The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.

Dolutegravir

The FDA has approved dolutegravir for use in children weighing ≥ 30 kg. The approval was supported by data from a study of 46 treatment-experienced (but INSTI-naive) adolescents^{9,16} and 11 treatment-experienced (but INSTI-naive) children aged ≥ 6 years.¹⁷ The World Health Organization (WHO) recommends using dolutegravir in children weighing ≥ 20 kg. This recommendation is based on PK and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY). The Panel agrees with the WHO assessment that dolutegravir can be used in children weighing ≥ 20 kg (see the [dolutegravir](#) section);¹⁸

it has a very favorable safety profile and can be given once daily to treat INSTI-naive patients. Studies of dolutegravir are ongoing in children as young as 4 weeks of age.¹⁹

In a prospective surveillance study of birth outcomes among pregnant women on ART in Botswana, an increased risk of neural tube defects (NTDs) was observed among infants born to women who were receiving dolutegravir at the time of conception.^{20,21} These findings should be considered when deciding on an ART regimen for female adolescents of childbearing potential. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see [Table 6b](#) and [Adolescents and Young Adults with HIV](#)) and in the Perinatal Guidelines (see [Teratogenicity](#) and [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#)).

Recommendation:

- Dolutegravir plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for children and adolescents **aged ≥ 3 years and weighing ≥ 25 kg (AI*)**. The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.^{7,9,22}
- **Dolutegravir plus a two-NRTI backbone is recommended as an *Alternative* INSTI-based regimen for children aged ≥ 3 years and weighing ≥ 20 kg to < 25 kg (AI*). Data are limited on the efficacy and safety of using dolutegravir in this weight group, and dolutegravir PKs vary more among children in this weight group than among those weighing ≥ 25 kg.**
- Dolutegravir is **not recommended** for use in adolescents and women who are trying to conceive or who may become pregnant, due to concerns about a possible increased risk of NTDs.

Elvitegravir

Elvitegravir is an INSTI that is available as a single-drug tablet, an FDC tablet that contains elvitegravir/cobicistat/emtricitabine/TDF, and an FDC tablet that contains elvitegravir/cobicistat/emtricitabine/TAF. Both FDC tablets are approved by the FDA for use in ART-naive adults with HIV. Elvitegravir/cobicistat/emtricitabine/TAF is approved for use in ART-naive children and adolescents weighing ≥ 25 kg. Cobicistat is a specific, potent cytochrome P450 (CYP) 3A inhibitor that has no activity against HIV and is used as a PK enhancer, which allows for once-daily dosing of elvitegravir.

Recommendation:

- Elvitegravir/cobicistat/emtricitabine/TAF is recommended as a *Preferred* INSTI-based regimen for children and adolescents weighing ≥ 25 kg who have creatinine clearance (CrCl) ≥ 30 mL/min (AI*). The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and adolescent studies.²³⁻²⁸

Raltegravir

Raltegravir is approved by the FDA for treatment of infants and children weighing ≥ 2 kg, and it can be used starting at birth. It is available in film-coated tablets, chewable tablets, and single use packets of granules for oral suspension. Clinicians should consult with an expert in pediatric HIV infection when initiating raltegravir-based treatment regimens in neonates, infants, and very young children. Additional information can be found in [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#).

Recommendation:

- Raltegravir plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants and children from birth to age 3 years who weigh ≥ 2 kg and for children aged ≥ 3 years and weighing < 25 kg (AI*). It is an *Alternative* INSTI-based regimen for children aged ≥ 3 years and weighing ≥ 25 kg (AI*). The Panel bases this recommendation on data from randomized clinical trials in adults, and

pediatric studies that were performed largely in ARV-experienced children and adolescents.^{7,29-36} The Panel acknowledges that data regarding the efficacy of this agent in those aged <2 years are currently very limited.³⁷

- At this time, the Panel **does not recommend** once-daily dosing for initial therapy in children and infants.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Efavirenz (for children aged ≥ 3 months), etravirine (for children aged ≥ 6 years), nevirapine (for children aged ≥ 15 days), and rilpivirine (for children aged ≥ 12 years) have been approved by the FDA for treatment of HIV infection in pediatric patients. NNRTIs have a long half-life that allows for less-frequent drug administration, a lower risk of dyslipidemia and fat maldistribution than some agents in the PI class, and, generally, a lower pill burden than PIs. However, a single viral mutation can confer high-level drug resistance to all NNRTIs except etravirine, and cross-resistance to other NNRTIs is common. Rare, but serious and potentially life-threatening, skin and hepatic toxicity can occur with the use of all NNRTI drugs, but these AEs are most frequently observed in patients taking nevirapine, at least among adults with HIV. NNRTIs have the potential to interact with other drugs that are also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted-PI regimens. [Table 8](#) lists the advantages and disadvantages of using NNRTIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information for each drug.

Efavirenz

Although efavirenz dosing recommendations are available for patients aged ≥ 3 months and weighing ≥ 3.5 kg, the Panel does not endorse the use of this drug in infants and children aged 3 months to 3 years because the PKs of efavirenz in very young patients can be highly variable.

Recommendation:

- Efavirenz plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for initial treatment of HIV in children aged ≥ 3 years (**AI***). The Panel bases this recommendation on data from studies that evaluated the efficacy and tolerability of this drug in adults and children.^{22,29,38-56}

Nevirapine

There are extensive clinical and safety data for the use of nevirapine in children with HIV, and nevirapine has shown ARV efficacy when used as a component in a variety of combination regimens.^{1,5,6,57-61} Nevirapine has also been used extensively as prophylaxis for the prevention of HIV transmission in young infants during the peripartum period and during breastfeeding. The safety and PKs of nevirapine have been studied at the low doses of the drug that are used for prophylaxis. There is currently less information available from studies in very young infants about the safety and PKs of the higher nevirapine doses that are necessary for treatment. Early testing of infants allows HIV infection to be confirmed before 14 days of age. In these cases, the Panel recommends the use of nevirapine as a *Preferred* NNRTI when a clinician plans to initiate treatment prior to age 14 days. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcomes compared to starting after age 14 days. Clinicians should consult an expert in pediatric HIV infection when considering the use of nevirapine in infants aged <14 days. Additional considerations regarding the use of nevirapine in infants aged <14 days can be found in [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#).

Recommendation:

- Nevirapine plus a two-NRTI backbone is recommended as a *Preferred* NNRTI-based regimen in infants aged <14 days and an *Alternative* NNRTI-based regimen for children aged ≥ 14 days to <3 years (**AI**). A change from nevirapine to LPV/r should be considered after 14 days of life and a post-gestational age of 42 weeks, as LPV/r has better clinical outcomes than nevirapine in children aged <3 years. The Panel recommends switching from nevirapine to LPV/r in these patients because nevirapine is associated with

rare occurrences of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, and rare (but potentially life-threatening) instances of hepatitis. Nevirapine also has a low barrier to resistance, and there is conflicting data about the virologic efficacy of nevirapine compared to *Preferred* regimens.^{1,5,6,59-71}

Rilpivirine

Rilpivirine is currently available both as a single-drug tablet and a once-daily FDC tablet that contains emtricitabine/rilpivirine/TDF. The single-drug tablet is approved for use in adolescents aged ≥ 12 years.

Recommendation:

- Rilpivirine plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for children and adolescents aged ≥ 12 years and weighing ≥ 35 kg who have HIV viral loads $\leq 100,000$ copies/mL (**AI***). The Panel bases this recommendation on the limited experience with rilpivirine in adolescents and the larger body of evidence in adults.^{45,72-76}

Protease Inhibitor-Based Regimens

Advantages of PI-based regimens include excellent virologic potency and a high barrier to drug resistance (since multiple mutations are required for a patient to develop resistance). However, because PIs are metabolized via hepatic enzymes, these drugs have the potential for multiple drug interactions. They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider when selecting a PI-based regimen for treatment-naïve children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly toxicities related to metabolic complications), the age of the child, and the availability of data regarding the use of the drug in children.

[Table 8](#) lists the advantages and disadvantages of using PIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.

Ritonavir is a potent inhibitor of the CYP3A4 isoenzyme and can be used in low doses as a PK booster when coadministered with some PIs, increasing drug exposure by prolonging the half-life of the boosted PI. Currently, only LPV/r is available as a coformulated product. In addition, the use of ritonavir boosting increases the risk of hyperlipidemia⁷⁷ and drug interactions.

Preferred and *Alternative* PIs are presented in **alphabetical** order below.

Atazanavir/Ritonavir

Atazanavir is a once-daily PI that was approved by the FDA in March 2008 for use in combination with a two-NRTI backbone in children aged ≥ 6 years. Atazanavir is most often boosted with ritonavir. Approval was extended in 2014 for use in infants and children aged ≥ 3 months and weighing ≥ 5 kg. Atazanavir administered in combination with cobicistat has been approved by the FDA for use in adults. The use of this combination in children and adolescents is under investigation, but no data are currently available.^{78,79}

Recommendation:

- ATV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for children aged ≥ 3 years and weighing < 25 kg, and as an *Alternative* PI-based regimen for children aged ≥ 3 months to < 3 years and children aged ≥ 3 years and weighing ≥ 25 kg (**AI***). This regimen has been shown to be virologically potent in adult and pediatric studies, and it has been well tolerated in pediatric studies. However, the oral powder formulations of ATV and RTV and the oral solution formulation of RTV can be cumbersome to administer.^{32,41,74,77,80-85}
- The Panel **does not recommend** the use of unboosted ATV.

Darunavir/Ritonavir

DRV/r is approved by the FDA for use in ARV-naïve and ARV-experienced children aged ≥ 3 years and weighing ≥ 10 kg. In addition, once-daily dosing of DRV/r is approved for ARV-naïve children aged ≥ 3 years and weighing ≥ 10 kg and ARV-experienced patients who do not have DRV resistance-associated mutations. Once-daily dosing of DRV/r was investigated during a substudy of a twice-daily dosing trial in children aged 3 years to < 12 years. This PK evaluation lasted only 2 weeks, after which the participants switched back to the twice-daily regimen.⁸⁶ FDA dosing recommendations are based on PK models from this study, but this dose has never undergone trials for clinical efficacy in this age group. A more recent study also suggested that once-daily DRV/r dosing is acceptable for children and adolescents. In this study, the plasma concentration-time curve for DRV/r was substantially lower than the mean value observed in adults; however, trough levels were similar. Because of these findings, and due to the lack of more information about the efficacy of once-daily DRV/r dosing in treatment-naïve and treatment-experienced children aged < 12 years, the Panel recommends a twice-daily dose of DRV/r in children aged > 3 years to < 12 years.⁸⁷

Recommendation:

- DRV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for children aged ≥ 3 years and weighing ≥ 10 kg but < 25 kg, and as an *Alternative* PI-based regimen for children aged ≥ 3 years and weighing ≥ 25 kg (**AI***). The Panel bases these recommendations on the virologic potency shown by DRV/r in adult and pediatric studies, and this combination's high barrier to development of drug resistance and excellent toxicity profile in adults and children.^{32,87-94}
- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of an *Alternative* PI-based regimen in treatment-naïve children and adolescents weighing ≥ 40 kg (**AI***).
- Twice-daily dosing of DRV/r should be used for children aged ≥ 3 years to < 12 years.
- Twice-daily dosing of DRV/r should be used if the following darunavir resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

Lopinavir/Ritonavir

LPV/r is approved to treat HIV infection in infants and children with a postmenstrual age ≥ 42 weeks and postnatal age ≥ 14 days. Once-daily LPV/r dosing is approved by the FDA for initial therapy in adults,⁹⁵ but PK data in children do not support a recommendation for once-daily dosing.⁹⁶⁻⁹⁸

Recommendation:

- LPV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for infants with a postmenstrual age ≥ 42 weeks and postnatal age ≥ 14 days to < 3 years (**AI**) and as an *Alternative* PI-based regimen in children aged ≥ 3 years (**AI***). This regimen has been shown to be virologically potent in adult and pediatric studies and has been well tolerated in pediatric studies.^{22,43,80,81,88,95-97,99-103}

Selection of Dual-Nucleoside Reverse Transcriptase Inhibitor Backbone as Part of Initial Combination Therapy

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, eight NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, TDF, and TAF) are approved by the FDA for use in children aged < 13 years. Dual-NRTI combinations that have been studied in children include:

- Zidovudine used in combination with abacavir, didanosine, or lamivudine
- Abacavir used in combination with lamivudine, stavudine, or didanosine

- Emtricitabine used in combination with stavudine or didanosine
- TDF used in combination with lamivudine or emtricitabine
- TAF used in combination with emtricitabine^{27,51,82,104-108}

The Panel **no longer recommends** using didanosine or stavudine as part of ARV regimens for children due to the significant toxicities observed when using these drugs and the availability of safer agents. The advantages and disadvantages of different dual-NRTI backbone options that are recommended for initial therapy are listed in [Table 8](#). See [What Not to Start](#) for more information. Also, see [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.

In the dual-NRTI regimens listed below, lamivudine and emtricitabine are interchangeable. Both lamivudine and emtricitabine are well tolerated and have few AEs. Emtricitabine is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine used in combination with abacavir or TDF or zidovudine). The main advantage of emtricitabine over lamivudine is that it can be administered once-daily as part of an initial regimen. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs, a modest decrease in susceptibility to abacavir, and improved susceptibility to zidovudine and TDF based on decreased viral fitness.^{109,110}

Dual-Nucleoside Reverse Transcriptase Inhibitor Backbone Regimens (in Alphabetical Order)

Abacavir in Combination with Lamivudine or Emtricitabine

Abacavir is approved for use in children aged ≥ 3 months when administered as part of an ART regimen.

Recommendation:

- Abacavir plus lamivudine or emtricitabine is recommended as the *Preferred* dual-NRTI combination for children aged ≥ 3 months (**AI**). Studies of adults and children have reported virologic efficacy and favorable toxicity profiles for these combinations.^{30,111-118}
- Once-daily dosing of abacavir is recommended when using the pill formulation. Twice-daily dosing of liquid abacavir is recommended for initial therapy; a change to once-daily dosing can be considered for clinically stable patients with undetectable viral loads and stable CD4 cell counts.¹¹⁹⁻¹²²

Tenofovir Alafenamide in Combination with Emtricitabine

TAF is an oral prodrug of tenofovir. It is approved by the FDA as a component of an FDC tablet that also contains elvitegravir, cobicistat, and emtricitabine for the treatment of HIV in ARV-naive individuals weighing ≥ 25 kg who have an estimated CrCl ≥ 30 mL/min. Additional safety and PK data are available for children aged 6 years to < 12 years who are receiving this FDC tablet.²⁸ An FDC tablet that contains emtricitabine/TAF (Descovy) is also available.

Recommendation:

- Emtricitabine/TAF is recommended as a *Preferred* dual-NRTI combination in children and adolescents weighing ≥ 25 kg who have estimated CrCl ≥ 30 mL/min when this combination is used with an INSTI or NNRTI; this combination is considered a *Preferred* dual-NRTI combination when used with a PI in children and adolescents weighing ≥ 35 kg who have estimated CrCl ≥ 30 mL/min (**AI***). This combination is also recommended as a *Preferred* drug combination when used in the single-tablet regimen elvitegravir/cobicistat/emtricitabine/TAF for children and adolescents weighing ≥ 25 kg (**AI***). The Panel makes these recommendations because TAF has a lower risk of renal and bone AEs than TDF.^{25,123}
- Emtricitabine/TAF is neither approved by the FDA nor recommended for use in combination with a

boosted PI in children weighing <35 kg, because this combination has not been adequately studied in this age and weight group.

Tenofovir Disoproxil Fumarate in Combination with Lamivudine or Emtricitabine

TDF is approved by the FDA for use in children and adolescents aged ≥ 2 years when administered as part of an ART regimen. Decreases in bone mineral density (BMD) have been observed in adults and children receiving TDF, but the clinical significance of these decreases is unknown.^{105-108,124,125} Before starting treatment, clinicians should consider whether the benefits of using TDF outweigh the potential risks of decreased BMD.¹²⁶

Recommendation:

- TDF plus lamivudine or emtricitabine is recommended as an *Alternative* dual-NRTI combination for children aged ≥ 2 years to 12 years (**AI***). The Panel bases this recommendation on the virologic efficacy and ease of dosing of these combinations.^{105-108,112-115,127-132}

Zidovudine in Combination with Abacavir

Zidovudine plus abacavir had lower rates of viral suppression and a greater number of toxicities that lead to regimen modification than did abacavir plus lamivudine in a European pediatric study.^{104,111}

Recommendation:

- Zidovudine plus abacavir is recommended as an *Alternative* dual-NRTI combination for children aged ≥ 3 months (**BII**).

Zidovudine in Combination with Lamivudine or Emtricitabine

Zidovudine is available as a syrup, a capsule, and a tablet, and it is also available in injectable/intravenous preparations. It is approved by the FDA for treatment in infants aged ≥ 4 weeks and prophylaxis in newborns.

Recommendation:

- Zidovudine plus lamivudine or emtricitabine is recommended as a *Preferred* dual-NRTI combination for infants and children from birth to age ≤ 6 years, and an *Alternative* combination in children aged ≥ 6 years and adolescents (**AI***). The Panel bases these recommendations on the extensive experience and favorable safety profiles for these combinations. There is extensive experience with these dual-NRTI backbones in children, and they have been shown to have favorable safety profiles. However, twice-daily dosing is required for zidovudine in children aged ≥ 6 years. Other NRTIs that only require once-daily dosing in children aged ≥ 6 years are available.^{116,133-135}
- Zidovudine plus abacavir is recommended as an *Alternative* dual-NRTI combination for use in children aged ≥ 3 months (**BII**). In children aged ≥ 6 years and adolescents who are not sexually mature (i.e., those with SMRs 1–3), the Panel recommends zidovudine plus lamivudine or emtricitabine as an *Alternative* dual-NRTI combination (**BII**).

Figure 1. Preferred Regimen by Age, Weight and Drug Class

		Patient Age and Weight Class				
		Birth to <14 Days of Age ^{a,b,c}	Children Aged ≥14 Days to <3 Years	Children Aged ≥3 Years and Weighing <25 kg	Children Aged ≥3 Years and Weighing ≥25 kg	Adolescents Aged ≥12 Years and Weighing ≥25 kg
INSTI-Based Regimens		Two NRTIs plus RAL ^c				
					Two NRTIs plus BIC ^d	
					Two NRTIs plus DTG ^e	
					Two NRTIs plus EVG/COBI ^f	
NNRTI-Based Regimens	Two NRTIs plus NVP ^{a,g}					
PI-Based Regimens			Two NRTIs plus LPV/r ^b			
				Two NRTIs plus ATV/r		
				Two NRTIs plus DRV/r ^h		

^a If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are the *Preferred* agents because they are the only options with dosing information available for this age group. However, available clinical trial data does not suggest that initiating treatment within the first 14 days of life is more beneficial than starting treatment after 14 days of age. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#). Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) of 42 weeks; LPV/r has produced better clinical outcomes in studies of children aged <3 years than NVP. Data are limited on the clinical outcomes of using RAL in infants and children aged <2 years.

^b LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age ≥14 days.

^c RAL can be used in infants weighing ≥2 kg. RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered to infants and children from birth to age 2 years.

^d BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF and is recommended as a *Preferred* regimen for adolescents aged ≥12 years and weighing ≥25 kg. It is recommended as an *Alternative* regimen for children aged ≥6 years and weighing ≥25 kg.

^e DTG is recommended as a *Preferred* regimen only for children and adolescents aged ≥3 years and weighing ≥25 kg. It is recommended as an *Alternative* regimen in children aged ≥3 years and weighing 20 kg to <25 kg. For children weighing <20 kg, the use of RAL can be considered when an INSTI-based regimen is desired.

^f EVG is currently recommended only as a component of FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as a *Preferred* regimen for children and adolescents weighing ≥35 kg, and as an *Alternative* regimen for children and adolescents weighing ≥25 kg.

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

^h Once-daily DRV should not be used in children aged <12 years or weighing <40 kg. Once-daily DRV should also not be used if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is recommended as an *Alternative* drug combination for children aged ≥6 years to <12 years, because there are other drugs that can be administered once daily. This combination is considered a *Preferred* option for adolescents aged ≥12 years with SMR 1–3 when once-daily administration is possible.

Key to Acronyms: ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; 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; SMR = sexual maturity rating; TAF = tenofovir alafenamide

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

An ART regimen for treatment-naive children is generally made up of a two-NRTI backbone and either one NNRTI **or** one INSTI **or** one PI boosted with RTV or COBI. *Preferred* regimens are designated based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens have also demonstrated efficacy, but clinical experience with these regimens is limited or these regimens are more difficult to administer than *Preferred* regimens. Regimens should be tailored to the individual patient by weighing the advantages and disadvantages of each combination. Many agents have multiple formulations and age and weight recommendations. Please consult [Appendix A: Pediatric Antiretroviral Drug Information](#) for additional information and recommended dosages and formulations (see [Table 8](#) below).

Children who are receiving effective and tolerable ART regimens can continue using those regimens as they age, even if the combinations they are receiving are no longer *Preferred* regimens.

Preferred Regimens			
Age	Regimens	FDC Available (see Fixed-Dose Combinations)	
Infants, Birth to Age <14 Days ^{a,b}	Two NRTIs plus NVP	No	
	Weight ≥2 kg	Two NRTIs plus RAL ^c	No
Children Aged ≥14 Days to <3 Years	Two NRTIs plus LPV/r	No	
	Weight ≥2 kg	Two NRTIs plus RAL ^c	No
Children Aged ≥3 Years	Weight <25 kg	Two NRTIs plus ATV/r	No
		Two NRTIs plus twice-daily DRV/r ^d	No
		Two NRTIs plus RAL ^c	No
	Weight ≥25 kg	Two NRTIs plus DTG ^e	Yes
		Two NRTIs plus EVG/COBI ^f	Yes
Adolescents Aged ≥12 Years with SMR 1–3	Weight ≥25 kg	Two NRTIs plus BIC ^g	Yes
Adolescents Aged ≥12 Years with SMR 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Regimens			
Age	Regimens	FDC Available	
Children Aged ≥14 Days to <3 Years	Two NRTIs plus NVP ^h	No	
Children Aged ≥3 Months to <3 Years	Two NRTIs plus ATV/r	No	
Children Aged ≥3 Years	Weight ≥20 kg to <25 kg	Two NRTIs plus DTG ^e	No
Children Aged ≥3 Years	Weight ≥25 kg	Two NRTIs plus ATV/r	No
		Two NRTIs plus DRV/r ^d	No
		Two NRTIs plus RAL ^c	No
Children Aged ≥3 Years	Two NRTIs plus EFV ⁱ	No ^j	
	Two NRTIs plus LPV/r	No	
Children Aged ≥6 Years to <12 Years	Weight ≥25 kg	Two NRTIs plus BIC ^g	Yes
Adolescents Aged ≥12 Years with SMR 1–3	Weight ≥35 kg	Two NRTIs plus RPV ^k	Yes
Adolescents Aged ≥12 Years with SMR 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs			
Age	Dual-NRTI Backbone Options	FDC Available	
Children, Birth to Age <3 Months	ZDV plus (3TC or FTC) ^l	No ^j	
Children Aged ≥3 Months to <6 Years	ABC plus (3TC or FTC) ^m	Yes	
	ZDV plus (3TC or FTC) ^l	Yes	
Children and Adolescents Aged ≥6 Years with SMR 1–3	ABC plus (3TC or FTC) ^m	Yes	
	Weighing ≥25 kg and receiving a regimen that contains an INSTI or an NNRTI	FTC/TAF ⁿ	Yes

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children,
continued

Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs, continued		
Age	Dual-NRTI Backbone Options	FDC Available
Adolescents Aged ≥ 12 Years with SMR 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines	Yes
Alternative Dual-NRTI Backbone Options for Use in Combination with Other Drugs		
Age	Dual-NRTI Backbone Options	FDC Available
Children Aged ≥ 3 Months	ZDV <u>plus</u> ABC	No
Children Aged ≥ 2 Years to 12 Years	TDF <u>plus</u> (3TC <u>or</u> FTC) ^a	Yes
Children and Adolescents Aged ≥ 6 Years and SMR 1–3	ZDV <u>plus</u> (3TC <u>or</u> FTC) ^l	Yes

^a If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are *Preferred* agents because they are the only options with dosing information available for this age group. While many pediatric experts favor initiating ART as soon as possible after birth in order to limit the establishment of viral reservoirs, available clinical trial data does not suggest that initiating treatment within the first 14 days of life leads to better clinical outcomes than initiating treatment after 14 days of age. Clinicians should consult an expert in pediatric HIV infection before initiating treatment in infants aged < 14 days. Additional considerations regarding the use of NVP or RAL in infants aged < 14 days can be found in [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#). Switching from NVP to LPV/r should be considered when the infant is aged ≥ 14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth); LPV/r has produced better clinical outcomes in studies of children aged < 3 years than NVP. Data are limited on the clinical outcomes of using RAL in infants and children aged < 2 years.

^b LPV/r should not be administered to neonates before a postmenstrual age 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 from birth to age 2 years. No dosing information is available for preterm infants or those with a weight of < 2 kg at birth.

^d DRV should only be used in children weighing ≥ 10 kg. Once-daily DRV should not be used in children aged < 12 years or weighing < 40 kg. Once-daily DRV should also not be used when any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is recommended as an *Alternative* drug combination for children aged ≥ 6 years to < 12 years and weighing > 25 kg, because there are other drugs that can be administered once daily and that are better tolerated. Note that DRV/r can be administered once daily in adolescents aged ≥ 12 years and weighing ≥ 40 kg who are not sexually mature (SMR 1–3).

^e DTG is recommended as a *Preferred* agent for children and adolescents aged ≥ 3 years and weighing ≥ 25 kg. It is recommended as an *Alternative* agent in children aged ≥ 3 years and weighing 20 kg to < 25 kg. An FDC tablet containing ABC/DTG/3TC (Triumeq) is available for children weighing ≥ 25 kg.

^f EVG is currently recommended only as a component of FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as a *Preferred* regimen for children and adolescents weighing ≥ 35 kg, and as an *Alternative* regimen for children and adolescents weighing ≥ 25 kg.

^g BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF and is recommended as a *Preferred* regimen for adolescents aged ≥ 12 years and weighing ≥ 25 kg. It is recommended as an *Alternative* regimen for children aged ≥ 6 years and weighing ≥ 25 kg.

^h NVP should not be used in post-pubertal girls with CD4 cell counts $> 250/\text{mm}^3$, unless the benefit clearly outweighs the risk. NVP is approved by the FDA for treatment of infants aged ≥ 15 days.

ⁱ EFV is approved by the FDA for use in children aged ≥ 3 months and weighing ≥ 3.5 kg, but it **is not recommended** by the Panel for initial therapy in children aged ≥ 3 months to 3 years. An FDC tablet containing EFV/FTC/TDF (Atripla) and EFV 600 mg/3TC/TDF (Symfi) is available. See [efavirenz](#) section for information about use of the FDC EFV 400 mg/3TC/TDF (Symfi Lo).

^j FDA-approved FDCs are not included in this table when they are not approved for use in the specific patient populations being discussed.

^k RPV should be administered to adolescents aged ≥ 12 years and weighing ≥ 35 kg who have initial viral loads $\leq 100,000$ copies/mL. FDC tablets containing FTC/RPV/TAF (Odefsey) and FTC/RPV/TDF (Complera) are available.

^l An FDC containing 3TC/ZDV (Combivir and generic) is available.

^m An FDC containing ABC/3TC (Epzicom and generic) is available.

ⁿ FTC/TAF is recommended as a *Preferred* combination for children and adolescents weighing ≥ 25 kg; an FDC containing FTC/TAF is available. FTC/TAF is approved by the FDA for children weighing ≥ 25 kg when used in the single-tablet regimen EVG/COBI/FTC/TAF or as TAF/FTC in combination with an NNRTI or INSTI. FTC/TAF plus a boosted PI is only recommended for use in children and adolescents weighing ≥ 35 kg.

^o An FDC containing FTC/TDF (Truvada) is available.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; **BIC = bictegravir**; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; 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; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (page 1 of 4)

See [Appendix A: Pediatric Antiretroviral Drug Information](#) and [Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios](#) in the [Adult and Adolescent Antiretroviral Guidelines](#) for more information.

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order	All INSTIs	INSTI Class Advantages: <ul style="list-style-type: none"> • Few drug-drug interactions • Well-tolerated 	INSTI Class Disadvantages: <ul style="list-style-type: none"> • Limited data on pediatric dosing or safety
	BIC	Once-daily administration Can give with or without food Available in FDC tablets (see Fixed-Dose Combinations)	FDC tablet is not recommended for patients with hepatic impairment or an estimated creatinine clearance <30 mL/min FDC tablet should not be coadministered with rifampin or dofetilide
	DTG	Once-daily administration Can give with food Available in FDC tablets (see Fixed-Dose Combinations) 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 of DTG CNS side effects, particularly sleep disturbances and possible increased risk of neural tube defects in infants born to women who were receiving dolutegravir at the time of conception
	EVG	Once-daily administration Available in FDC tablets (see Fixed-Dose Combinations)	Among INSTIs, EVG has the lowest barrier to the development of resistance. If EVG is administered with COBI, there is potential for multiple drug interactions because COBI is metabolized by hepatic enzymes (e.g., CYP3A4). COBI inhibits tubular secretion of creatinine, and this may result in increased serum creatinine but normal glomerular clearance.
	RAL	Can give with food Available in tablet, chewable tablet, and powder formulations Once-daily administration (with RAL HD) can be used for treatment-naïve or virologically suppressed children weighing ≥50 kg.	Potential for rare systemic allergic reaction or hepatitis Granule formulation requires a multistep preparation before administration; caregiver must be taught how to properly prepare this formulation.
NNRTIs In Alphabetical Order	All NNRTIs	NNRTI Class Advantages: <ul style="list-style-type: none"> • Long half-life • Lower risk of dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking the solid formulation; easier to use and adhere to than PI-based regimens 	NNRTI Class Disadvantages: <ul style="list-style-type: none"> • A 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. All NNRTIs pose this risk, but the risk is greatest with NVP. • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children^a (page 2 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs In Alphabetical Order, continued	EFV	Once-daily administration Available in the FDC tablets (see Fixed-Dose Combinations) Potent ARV activity Can give with food (but avoid high-fat meals) Capsules can be opened and added to food.	Neuropsychiatric AEs (bedtime dosing is recommended to reduce CNS effects) Rash (generally mild) No commercially available liquid formulation Limited data on dosing for children aged <3 years No data on dosing for children aged <3 months
	NVP	Liquid formulation is available. Dosing information for young infants is 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 m ² Low barrier for resistance
	RPV	Once-daily dosing Available in FDC tablets (see Fixed-Dose Combinations)	Should not use in patients with HIV viral loads >100,000 copies/mL Must be taken with a ≥500 kcal meal at a consistent time each day; this may affect adherence. Low barrier for resistance
PIs In Alphabetical Order	All PIs	PI Class Advantages: <ul style="list-style-type: none"> • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well-documented. • Resistance to PIs requires multiple mutations. • When combined with a dual-NRTI backbone, a regimen containing a PI targets HIV at two steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes. 	PI Class Disadvantages: <ul style="list-style-type: none"> • Metabolic complications, including dyslipidemia, fat maldistribution, and insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI-based or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence • Most PIs require RTV boosting, resulting in drug interactions that are associated with RTV.
	Boosted ATV	Once-daily dosing Powder formulation is available. ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	No liquid formulation Should be administered with food) Indirect hyperbilirubinemia is common, but asymptomatic. Scleral icterus may be distressing to the patient, which may affect adherence. Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG). RTV is associated with a large number of drug interactions.

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children^a (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	Boosted DRV	Can be used once daily in children aged ≥ 12 years Liquid formulation is available. DRV requires a boosting agent. Available in FDC tablets (see Fixed-Dose Combinations)	Pediatric pill burden high with current tablet dose formulations Should be administered with food Must be boosted to achieve adequate plasma concentrations Contains sulfa moiety. The potential for cross-sensitivity between DRV and other drugs in sulfonamide class is unknown. RTV is associated with a large number of drug interactions. Can only be used once daily in the absence of certain PI-associated resistance mutations
	LPV/r	LPV is only available coformulated with RTV in liquid and tablet formulations. Tablets can be given without regard to food, but they may be better tolerated when taken with meal or snack.	Poor palatability of liquid formulation (bitter taste), although the palatability of the FDC is better than RTV alone Liquid formulation should be administered with food. RTV is associated with a large number of drug interactions. Should not be administered to neonates before a postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) of 42 weeks and a postnatal age ≥ 14 days Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Dual-NRTI Backbones In Alphabetical Order	ABC plus (3TC or FTC)	Palatable liquid formulations Can give with food Available in FDC tablets (see Fixed-Dose Combinations)	Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
	FTC/TAF for children aged ≥ 6 years	Once-daily dosing Small tablet size Lower risk of TFV-associated renal and bone toxicity with TAF than with TDF in adults Available in FDC tablets (see Fixed-Dose Combinations)	Limited data on the safety and efficacy of this combination in children Increased lipid levels
	TDF plus (3TC or FTC) for adolescents with SMR 4 or 5	Once-daily dosing for TDF Resistance is slow to develop. Lower risk of mitochondrial toxicity than other NRTIs Can give with food Available as reduced-strength tablets and oral powder for use in younger children Available in FDC tablets (see Fixed-Dose Combinations)	Limited pediatric experience Potential bone and renal toxicity Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV.

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children^a (page 4 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order, continued	ZDV plus (3TC or FTC)	Extensive pediatric experience Coformulations of ZDV and 3TC are available (Combivir and generic) for children weighing ≥30 kg. Palatable liquid formulations Can give with food FTC is available as a palatable liquid formulation that can be administered once daily.	Bone marrow suppression with ZDV Lipoatrophy with ZDV
	ZDV plus ABC	Palatable liquid formulations Can give with food	Risk of ABC HSRs; perform HLA-B*5701 screening before initiation of ABC treatment. Bone marrow suppression and lipoatrophy with ZDV

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; **BIC = bictegravir**; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; CYP = cytochrome P450; ddl = didanosine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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