What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children

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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 viral load. 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 available) with the drug or regimen, preferably in children as well as adults;
- The extent of pediatric experience with a specific drug or regimen;
- The incidence and types of short-term and long-term drug toxicity in people who are taking the drug or regimen, focusing on toxicities that are reported in children;
- The 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*
- The 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-naive 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 appropriate drug exposure. 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 or drug combinations have disadvantages when compared with *Preferred* regimens. Drugs or drug combinations may be classified as *Alternative* for use in treatment-naive children if they are less effective or durable than a *Preferred* regimen in adults or children; if specific concerns exist about toxicity, dosing, formulation, administration, or interaction; or if experience with the use of these drugs or drug combinations in children is limited.

Factors to Consider When Selecting an Initial Regimen

An antiretroviral (ARV) regimen for children should generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an active drug from one of the following classes: an integrase strand transfer inhibitor (INSTI), a 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 drug-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 is infants aged <14 days. 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 HIV Infection.

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, 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, and palatability problems. Counseling patients and caregivers about adherence to therapy is essential for successful ART. The Panel recommends rapid initiation of ART (defined as initiating ART immediately or within days of diagnosis).

Emtricitabine (FTC), lamivudine (3TC), 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 drug-resistance testing, 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 (NVP)-based regimen in infants and children aged 2 to 35 months, regardless of maternal or infant exposure to peripartum, single-dose NVP prophylaxis. In children with prior NVP 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 NVP-based regimen. For children with no prior NVP 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 NVP-based regimen.[1]
- Those in the NVP group demonstrated greater, but not statistically significant, improvements in CD4 counts and growth parameters. However, improvements in CD4 counts were maintained only up to 1 year after initiation of ART.[2] Similar improved immune and growth parameters were reported in the Neviraoine Resistance NEVEREST study, where these parameters were compared in children who switched to a NVP-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 (EFV) 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-naive children aged 30 days to <18 years (the study did not dictate the use of specific NNRTIs or PIs). 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 EFV and 38% received NVP. 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 ARV 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 ARV regimen.[6] Children were aged 2 months to <6 years and had no perinatal exposure to NVP. Selection of the NNRTI was based on age (children aged <3 years received NVP, and those aged >3 years primarily received EFV). The proportion of children with viral loads <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-naive adolescents.[9]

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

- Newborns aged <14 days: NVP
- Newborns aged <4 weeks and weighing ≥2 kg: Raltegravir (RAL)
- Neonates aged ≥14 days to <4 weeks: LPV/r
- Infants and Children aged ≥4 weeks and weighing ≥3 kg: Dolutegravir (DTG)
- Children aged ≥6 years and weighing ≥25 kg: DTG or Bictegravir (BIC). BIC is available only as a component of the fixed-dose combinations (FDC) tablet bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).

Alternative regimens are shown in Table 7 below.

Integrase Strand Transfer Inhibitor-Based Regimens

Four INSTIs—BIC, DTG, EVG, and RAL—are approved by the FDA for treating ARV-naive adults and children with HIV. INSTI-based regimens have quickly become the recommended regimens in adults because of their virologic efficacy, lack of drug interactions, and favorable toxicity profile. RAL is approved for the treatment of infants and children from birth onward with weights of ≥2 kg. DTG is approved by the FDA for use in infants and children ≥4 weeks and weighing ≥3 kg. The FDC tablet BIC/FTC/TAF (Biktarvy) is approved by the FDA for use in children weighing ≥25 kg. EVG has been studied in adolescents in two FDC regimens and in combination with two NRTIs and ritonavir (RTV) boosting. BIC and DTG, the second-generation INSTIs, have higher barriers to resistance than the first-generation INSTIs RAL and EVG [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.

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

Bictegravir

BIC/FTC/TAF was approved by the FDA in 2018 for use in adults and in 2019 for use in children or adolescents weighing ≥25 kg. It 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 (viral load <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 tablet.

BIC/FTC/TAF 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:

- BIC/FTC/TAF is recommended as a Preferred 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

DTG is approved by the FDA for use in infants and children ≥4 weeks and weighing ≥3 kg. This recommendation is based on PK and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY), as well as a study of treatment-experienced (but INSTI-naive) older children.[9,16,17]

In a prospective surveillance study of birth outcomes among pregnant women on ART in Botswana, a very small significant increase in the risk of neural tube defects (NTDs) was observed among infants born to women who were receiving DTG at the time of conception.[18–20] For additional information refer to the Perinatal Guidelines, see Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers.

Recommendation:

- DTG plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg **(AI*)**. The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and

pediatric studies.[7,9,21,22]

- In light of concerns about the potential increased risk of NTDs with the use of DTG, pediatric and adolescent care providers should discuss this risk with patients who are receiving or initiating DTG and their caregivers so they can make informed decisions about the use of DTG (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers in the Perinatal Guidelines). For additional information, refer to the Perinatal Guidelines; see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Elvitegravir

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

Recommendation:

- EVG/c/FTC/TAF is recommended as an *Alternative* 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 but does not recommend it as a Preferred INSTI-based regimen because of the lower barrier to resistance of EVG compared to BIC or DTG, and the potential for multiple drug–drug interactions from COBI.[23–27]

Raltegravir

RAL 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 RAL-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 HIV Infection.

Recommendation:

- RAL plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants and children from birth to age 4 weeks who weigh ≥2 kg. **(AI*)**. It is an *Alternative* INSTI-based regimen for children aged ≥4 weeks because of its twice-daily dosing requirement and lower barrier to resistance compared with other INSTIs **(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.[7,28–35,36]

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

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

EFV (for children aged ≥3 months), etravirine (ETR; for children aged ≥6 years), NVP (for children aged ≥15 days), and rilpivirine (RPV; 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 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 ETR, 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 NVP, 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 below lists the advantages and disadvantages of using NNRTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information for each drug.

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

Efavirenz

Although EFV 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 EFV in very young patients can be highly variable. There may be a role for use of EFV in children <3 years of age who have HIV and TB co-infection as EFV is one of the few ARVs with minimal drug-drug interaction.[37]

Recommendation:

- EFV 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.[21,28,38–55]

Nevirapine

Extensive clinical and safety data exist for the use of NVP in children with HIV, and NVP has shown ARV efficacy when used as a component in a variety of combination regimens.[1,5,6,56–60] NVP also has 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 NVP have been studied at the low doses of the drug that are used for prophylaxis. Less information is currently available from studies in very young infants about the safety and PKs of the higher NVP doses that are necessary for treatment.

Early testing of infants allows HIV infection to be confirmed before 14 days of age. The Panel recommends the use of NVP as a *Preferred* NNRTI when a clinician plans to initiate treatment prior to age 14 days. However, no clinical trial data currently suggest 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 NVP in infants aged <14 days. Additional considerations regarding the use of NVP in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Recommendation:

- NVP 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)**. Clinicians should consider switching from NVP to LPV/r or RAL in children aged ≥14 days to <4 weeks, because these drugs are the *Preferred* ARV agents for this age bracket. LPV/r has better clinical outcomes than NVP in children aged <3 years. The Panel recommends switching from NVP to LPV/r in these patients, because NVP is associated with rare occurrences of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, and rare (but potentially life-threatening) instances of hepatitis. NVP also has a low barrier to resistance, and conflicting data exist about the virologic efficacy of NVP-based regimens compared to the efficacy of *Preferred* regimens. [1,5,6,58–68]

Rilpivirine

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

Recommendation:

- RPV 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 ≤100,000 copies/mL **(AI*)**. The Panel bases this recommendation on the limited experience with RPV in adolescents and the larger body of evidence in adults.[45,69–72]

Protease Inhibitor-Based Regimens

Advantages of PI-based regimens include excellent virologic potency and a high barrier to drug resistance (because 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 also may be associated with metabolic complications, such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider when selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, the availability of palatable pediatric formulations, the drug interaction profile, the 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 below lists the advantages and disadvantages of using PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

RTV 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 RTV boosting increases the risk of hyperlipidemia[73] and drug interactions. COBI is an alternative CYP3A4 inhibitor that also can be used as a booster. It is available in a single-drug tablet and in coformulations with ATV and with DRV. Currently, the single-drug tablet is approved by the FDA for administration with ATV in children weighing ≥35 kg and for administration with DRV in children weighing ≥40 kg.

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

Atazanavir Boosted with Ritonavir or Cobicistat

ATV 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. ATV is most often boosted with RTV. Approval was extended in 2014 for use in infants and children aged ≥3 months and weighing ≥5 kg.[74,75] ATV administered in combination with COBI has been approved by the FDA for use in adults and, using the single-agent COBI tablet, in children weighing ≥35 kg.

Recommendation:

- ATV/r plus a two-NRTI backbone is recommended as a *Alternative* PI-based regimen for children aged ≥3 months **(AI*)**. ATV/c plus a two-NRTI backbone is an *Alternative* PI-based regimen for children weighing ≥35 kg. These regimens have been shown to be virologically potent in adult and pediatric studies and have 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.[31,41,71,73,76–81]
- The Panel **does not recommend** the use of unboosted ATV.

Darunavir Boosted with Ritonavir or Cobicistat

DRV/r is approved by the FDA for use in ARV-naive and ARV-experienced children aged ≥3 years and weighing ≥10 kg. In addition, once-daily dosing of DRV/r is approved for ARV-naive children aged ≥3 years and weighing ≥10 kg, and for 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.[82] 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 because of the lack of more information about the efficacy of once-daily DRV/r dosing in ARV-naive and ARV-experienced children aged <12 years, the Panel recommends a twice-daily dose of DRV/r in children aged >3 years to <12 years.[83] DRV administered in combination with COBI has been approved by the FDA for use in adults and, using the single-agent COBI tablet, in children weighing ≥40 kg.[84]

Recommendation:

- DRV/r plus a two-NRTI backbone is recommended as an *Alternative* PI-based regimen for children aged ≥3 years and weighing ≥10 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 the development of drug resistance and excellent toxicity profile in adults and children.[31,85–91]
- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of an *Alternative* PI-based regimen in ARV-naive 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 when the following DRV resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- DRV/c plus a two-NRTI backbone is recommended as an *Alternative* PI-based regimen for adolescents aged ≥12 years and weighing ≥40 kg who are not sexually mature.

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,[92] but PK data in children do not support a recommendation for once-daily dosing.[93,94]

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 <4 weeks **(AI)** and as an *Alternative* PI-based regimen in children aged ≥4 weeks **(AI*)**. This regimen has been shown to be virologically potent in adult and pediatric studies and has been well tolerated in pediatric studies. Although it is recommended only as a *Preferred* PI-based regimen for a narrow age range, use of LPV/r is supported by many Panel members as a *Preferred* PI-based regimen in children up to 3 years of age due to extensive experience with this drug and ease of administering a liquid formulation in infants and very young children. [21,43,76,77,85,92–99]

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 [ZDV], didanosine [ddI], 3TC, stavudine [d4T], abacavir [ABC], FTC, 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 the following:

- ZDV used in combination with ABC, ddI, or 3TC
- ABC used in combination with 3TC, d4T, or ddI
- FTC used in combination with d4T or ddI
- TDF used in combination with 3TC or FTC
- TAF used in combination with FTC[27,51,78,100–104]

The Panel **no longer recommends** using ddI or d4T as part of ARV regimens for children because of the

significant toxicities observed when using these drugs and the availability of safer agents. The advantages and disadvantages of the different dual-NRTI backbone options that are recommended for initial therapy in children are listed in Table 8 below. 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 backbones listed below, 3TC and FTC are interchangeable. Both 3TC and FTC are well tolerated and have few AEs. FTC is similar to 3TC and can be substituted for 3TC as one component of a preferred dual-NRTI backbone (i.e., FTC used in combination with ABC, TDF, or ZDV). The main advantage of FTC over 3TC is that it can be administered once-daily as part of an initial regimen. Both 3TC and FTC select for the M184V resistance mutation, which is associated with high-level resistance to both drugs, a modest decrease in susceptibility to ABC, and improved susceptibility to ZDV and TDF as a result of decreased viral fitness.[105,106]

Dual-Nucleoside Reverse Transcriptase Inhibitor Backbones

Dual-NRTI combinations are presented in **alphabetical** order below.

Abacavir in Combination with Lamivudine or Emtricitabine

ABC is approved by the FDA for use in children aged ≥3 months when administered as part of an ARV regimen. Recent data suggest that ABC is safe in infants and children ≥1 month of age.

Recommendation:

- ABC plus 3TC or FTC is recommended as the *Preferred* dual-NRTI combination for children aged ≥1 month **(AI)**. Studies of adults and children have reported virologic efficacy and favorable toxicity profiles for these combinations.[29,107–114] Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on safety of ABC in infants when initiated at the age <3 months.[115–117]
- Once-daily dosing is recommended when using the pill formulation of ABC. Twice-daily dosing of liquid ABC 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 counts.[118–121]

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 EVG, COBI, and FTC 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.[26] An FDC tablet that contains FTC/TAF (Descovy) is also available.

Coadministration of TAF with boosted ATV, DRV, or LPV increase TAF exposure to concentrations that are higher than those seen with use of EVG/c/FTC/TAF. Because no data exist on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with COBI-boosted or RTV-boosted PIs in children weighing <35 kg cannot be assured and is not recommended.

Recommendation:

- FTC/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 also is recommended as a *Preferred* drug combination when used in the single-tablet regimen EVG/c/FTC/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.[27]

- FTC/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 ARV 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.[101–104,122,123] Before starting treatment, clinicians should consider whether the benefits of using TDF outweigh the potential risks of decreased BMD.[124]

Recommendation:

- TDF plus 3TC or FTC 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.[101–104,108–111,125–130]

Zidovudine in Combination with Abacavir

In a European pediatric study, patients who received ZDV plus ABC had lower rates of viral suppression and a greater number of toxicities that lead to regimen modification than patients who received ABC plus 3TC.[100,107] Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on the safety of ABC in infants when initiated at age <3 months.[115–117]

Recommendation:

- ZDV plus ABC is recommended as an *Alternative* dual-NRTI combination for children aged ≥1 months **(BII)**.

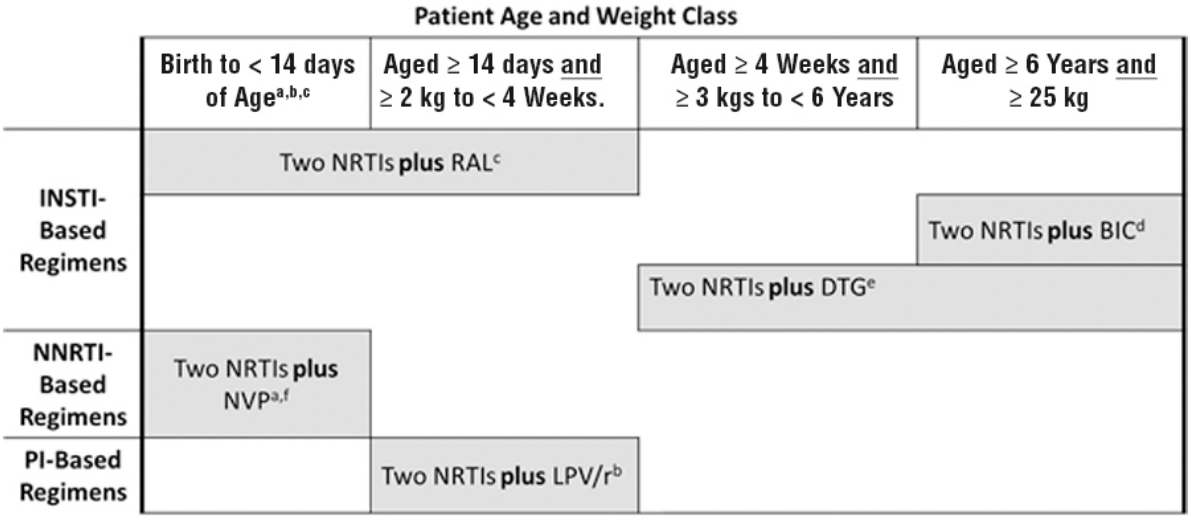
Zidovudine in Combination with Lamivudine or Emtricitabine

ZDV 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 of HIV in infants aged ≥4 weeks and for prophylaxis in newborns.

Recommendation:

- ZDV plus 3TC or FTC is recommended as a *Preferred* dual-NRTI combination for infants and children from birth to age ≤1 month, and an *Alternative* combination in children aged ≥1 month and adolescents **(AI*)**. Twice-daily dosing is required for ages with ZDV. Other NRTIs that require only once-daily dosing in children aged ≥6 years are available.[112,131–133]
- In children aged ≥6 years and adolescents who are not sexually mature (i.e., those with SMRs of 1–3), the Panel recommends ZDV plus 3TC or FTC as an *Alternative* dual-NRTI combination **(BII)**.

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



[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 do 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 HIV Infection. 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] In general, LPV/r **should not be administered** to neonates before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days (see the Lopinavir/Ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information).

[c] RAL granules can be administered to infants and children weighing ≥2 kg from birth to age 2 years. Oral RAL granules can be used up to a dose of 100 mg in the 14 to <20 kg weight band. RAL pills or chewable tablets can be used in children aged ≥2 years. Chewable RAL tablets can be crushed and dispersed in liquid to infants as young as 4 weeks of age who weigh at least 3 kgs.

[d] BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF; this FDC tablet is recommended as a *Preferred* regimen for children weighing ≥25 kg.

[e] DTG is recommended as a *Preferred* agent for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg. DTG dispersible tablets can be administered in infants and children aged ≥4 weeks and weighing ≥3 kg DTG. Film-coated DTG tablets can be used in children weighing ≥14 kg. An FDC tablet that contains ABC/DTG/3TC (Triumeq) is available for children weighing ≥25 kg.

[f] NVP should not be used in post-pubertal girls with CD4 counts >250/mm^3, unless the benefit clearly outweighs the risk. NVP is approved by the FDA for the treatment of infants aged ≥15 days.

Key: ART = antiretroviral therapy; BIC = bictegravir; CD4 = CD4 T lymphocyte; DTG = dolutegravir; 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; TAF = tenofovir alafenamide

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children
An ARV 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. Regimens are designated *Preferred* based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens also have 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 doses and formulations (see Table 8 below).

Children who are receiving effective and tolerable ARV regimens can continue using those regimens as they age, even if the combinations they are receiving are no longer *Preferred* regimens. Please refer to Management of Children Receiving Antiretroviral Therapy sections for decisions about transitioning children to other regimens as they grow.

Preferred Initial Regimens Based on Age and Weight			
Age	**Weight Restriction**	**Regimens**	**FDC Available** (see Appendix A, Table 1)
Newborns, Birth to Age <14 Days[a,b]	None	Two NRTIs **plus** NVP	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Neonates ≥14 Days to Age <4 weeks	None	Two NRTIs **plus** LPV/r[b]	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Infants and children Aged ≥4 Weeks to <6 Years	≥3 kg	Two NRTIs **plus** DTG[d]	No
Children Aged ≥6 Years	≥25 kg	Two NRTIs **plus** BIC[e]	Yes
		Two NRTIs **plus** DTG[d]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Regimens			
Age	**Weight Restriction**	**Regimens**	**FDC Available** (see Appendix A, Table 1)
Neonates, infants and children Aged ≥14 Days to ≥3 Years	None	Two NRTIs **plus** NVP[f]	No
Infants and children Aged ≥4 Weeks to <3 Months	None	Two NRTIs **plus** LPV/r[b]	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Infants and children Aged ≥3 Months to <3 Years	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** DRV/r[g]	No
	None	Two NRTIs **plus** EFV[h]	No[i]
	≥25 kg	Two NRTIs **plus** EVG/c[j]	Yes
	None	Two NRTIs **plus** LPV/r[b]	
	None	Two NRTIs **plus** RAL[c]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** DRV/r[g]	No
	None	Two NRTIs **plus** EFV[h]	Yes
	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
	≥25 kg	Two NRTIs **plus** EVG/c[j]	Yes
	≥35 kg	Two NRTIs **plus** RPV[k]	Yes
		Two NRTIs **plus** ATV/c	No
	≥40 kg	Two NRTIs **plus** ATV/c[l]	Yes

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

Adolescents Aged ≥12 Years with SMRs of 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**
Neonates Birth to Age <3 Months	ZDV **plus** (3TC **or** FTC)[m]	No[j]
Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs, continued		
Age	**Dual-NRTI Backbone Options**	**FDC Available**
Neonates Birth to Age <1 Month	ZDV **plus** (3TC or FTC)[m]	No[j]
Infants and children Aged ≥1 Month to <6 Years	ABC **plus** (3TC **or** FTC)[n]	Yes
Children and Adolescents Aged ≥6 Years with SMRs of 1–3	ABC **plus** (3TC **or** FTC)[n]	Yes
	FTC/TAF[o] weighing ≥25 kg and receiving a regimen that contains an INSTI or an NNRTI)	Yes
Adolescents Aged ≥12 Years with SMRs of 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**
Infants and children Aged ≥1 Month to <6 Years	ZDV **plus** (3TC **or** FTC)[m]	No
	ZDV **plus** ABC[n]	No
Children Aged ≥2 Years to 6 Years	TDF **plus** (3TC **or** FTC)[p]	Yes
	ZDV **plus** (3TC or FTC)[m]	Yes
	ZDV **plus** ABC[n]	No
Children and Adolescents Aged ≥6 Years and SMRs of 1–3	ZDV **plus** (3TC **or** FTC)[m]	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 do 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 HIV Infection. 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] In general, LPV/r **should not be administered** to neonates before a postmenstrual age of 42 weeks and postnatal age ≥14 days (see the Lopinavir/Ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information).

[c] RAL granules can be administered to infants and children weighing ≥2 kg from birth to age 2 years. Oral RAL granules can be used up to a dose of 100 mg in the 14 to <20 kg weight band. RAL pills or chewable tablets can be used in children aged ≥2 years. Chewable RAL tablets can be crushed and dispersed in liquid to infants as young as 4 weeks of age who weight at least 3 kgs.

[d] BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF; this FDC tablet is recommended as a *Preferred* regimen for children weighing ≥25 kg.

[e] DTG is recommended as a *Preferred* agent for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg. DTG dispersible tablets can be administered in infants and children aged ≥4 weeks and weighing ≥3 kg DTG. Film-coated DTG tablets can be used in children weighing ≥14 kg. An FDC tablet that contains ABC/DTG/3TC (Triumeq) is available for children weighing ≥25 kg.

[f] NVP should not be used in post-pubertal girls with CD4 counts >250/mm^3, unless the benefit clearly outweighs the risk. NVP is approved by the FDA for the treatment of infants aged ≥15 days.

[g] 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).

[h] 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. FDC tablets that contain EFV/FTC/TDF (Atripla) and EFV 600 mg/3TC/TDF (Symfi) are available. See the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information for information about use of

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

the FDC EFV 400 mg/3TC/TDF (Symfi Lo).

[j] FDA-approved FDC tablets are not included in this table when they are not approved for use in the specific patient populations being discussed.

[j] EVG is currently recommended only as a component of FDC tablets. Tablets that contain EVG/c/FTC/TAF (Genvoya) are recommended as a *Alternative* regimen for children and adolescents weighing ≥25 kg due to multiple drug-drug interactions from the cobicistat and a lower barrier to the development of resistance to elvitegravir.

[k] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have initial viral loads ≤100,000 copies/mL. FDC tablets that contain FTC/RPV/TAF (Odefsey) and FTC/RPV/TDF (Complera) are available.

[l] DRV/c is available as part of an FDC tablet containing DRV/c/FTC/TAF (Symtuza) that has been approved by the FDA for use in children and adolescents weighing ≥40 kg.

[m] An FDC tablet that contains 3TC/ZDV (Combivir and generic) is available for use in children weighing ≥30 kg.

[n] ABC is not approved by the FDA for use in neonates and infants aged <3 months. Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on safety of ABC in infants when initiated at the age <3 months, see Abacavir. An FDC tablet that contains ABC/3TC (Epzicom and generic) is available for use in children weighing ≥25 kg.

[o] FTC plus TAF is recommended as a *Preferred* combination for children and adolescents weighing ≥25 kg; an FDC tablet that contains FTC/TAF (Descovy) is available. FTC/TAF is approved by the FDA for children weighing ≥25 kg when used in the single-tablet regimen EVG/c/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.

[p] An FDC tablet that contains FTC/TDF (Truvada) is available.

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; 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; the Panel = the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; 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:** • Few drug-drug interactions • Well tolerated	**INSTI Class Disadvantages:** • Limited data on pediatric dosing or safety Possible weight gain in adults, especially Black/African American women
	BIC	Once-daily administration Can give with or without food Available in FDC tablets (see Appendix A, Table 1)	The FDC tablet **is not recommended** for patients with hepatic impairment or an estimated CrCl <30 mL/min. The FDC tablet **should not be coadministered** with rifampin or dofetilide.
	DTG	Once-daily administration Can give with food Available in FDC tablets (see Appendix A, Table 1) Single-agent DTG pills are available in several doses and are small in size. DTG is available as dispersible tablets for suspension.	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 NTDs in infants born to women who were receiving DTG at the time of conception

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order, continued	EVG	Once-daily administration Available in FDC tablets (see Appendix A, Table 1)	Among INSTIs, EVG has the lowest barrier to the development of resistance. If EVG is coadministered with COBI, the potential exists 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 Chewable tablets can be crushed and mixed with various liquids for infants ≥4 weeks of age who weigh ≥3 kgs. Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥40 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:** • 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:** • 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, although these toxic effects have not been reported in neonates. • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	Once-daily administration Available in FDC tablets (see Appendix A, Table 1) 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 to resistance
	RPV	Once-daily dosing Available in FDC tablets (see Appendix A, Table 1)	Should not use in patients with 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 to resistance

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

PIs In Alphabetical Order	All PIs	**PI Class Advantages:** • 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 that contains a PI targets HIV at two steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.	**PI Class Disadvantages:** • 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
ARV Class	**ARV Agent(s)**	**Advantages**	**Disadvantages**
PIs In Alphabetical Order, continued	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 pre-existing conduction system defects (can prolong PR interval of ECG). RTV is associated with a large number of drug interactions.
	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 Appendix A, Table 1)	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 available only coformulated with RTV in liquid and tablet formulations. Tablets can be given without regard to food, but they may be tolerated better when taken with meal or snack.	Poor palatability of liquid formulation (bitter taste). 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 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) 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)

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

Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	Palatable liquid formulations Can give with food Available in FDC tablets (see Appendix A, Table 1)	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC.
	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 Appendix A, Table 1)	Limited data on the safety and efficacy of this combination in children Increased lipid levels
ARV Class	**ARV Agent(s)**	**Advantages**	**Disadvantages**
Dual-NRTI Backbones In Alphabetical Order, continued	TDF **plus** (3TC **or** FTC) for adolescents with SMRs of 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 Appendix A, Table 1)	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.
	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 and lipoatrophy with ZDV
	ZDV **plus** ABC	Palatable liquid formulations Can give with food	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC. Bone marrow suppression and lipoatrophy with ZDV

Key:: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CYP = cytochrome P450; ddI = didanosine; DRV = darunavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HD = high dose; 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; NTD = neural tube defect; 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 = triglyceride; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

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