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 May 22, 2018; last reviewed May 22, 2018)

Panel's Recommendations

- The selection of an initial regimen should be individualized based on several factors, including characteristics of the proposed regimen, patient characteristics, drug efficacy, potential adverse effects, patient and family preferences, and 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, including either an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor, plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone (AI*).
- Table 7 provides a list of Panel-recommended regimens that are designated as Preferred or Alternative; recommendations vary by age, weight, and sexual maturity rating.

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- Table 7 provides a list of Panel-recommended regimens that are designated as Preferred or Alternative; recommendations vary by 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 provide direct comparisons of 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 adult studies, 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 the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., syrups vs. powders), volume of syrups, and pill size/number of pills;
- 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-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 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 less 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/nucleotide reverse transcriptase inhibitors (NRTIs) plus one active drug from 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 characteristics of the proposed regimen, patient characteristics, and 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 of the recommendation for selecting a specific drug (except for infants aged <14 days). When FDA approvals are based solely on weight, the Panel has suggested an approximate age for administration. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Table 8. Additional information regarding advantages and disadvantages of drug combinations can be found in the Adult and Adolescent Guidelines. Specific information about 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, including the complexity of schedules and food requirements for different regimens, differing formulations, palatability problems, and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after assessment and counseling of caregivers about adherence to therapy.

Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have antiviral activity and efficacy against hepatitis B and should be considered for use in children with coinfection. For a comprehensive review of this topic, as well as hepatitis C and tuberculosis during HIV coinfection, see the Pediatric Opportunistic Infections Guidelines.

### Choosing Between an Integrase Strand Transfer Inhibitor-, a Non-Nucleoside Reverse Transcriptase Inhibitor-, or a Boosted Protease Inhibitor-Based Initial Regimen

Preferred regimens for initial therapy include INSTI-, NNRTI-, or boosted PI-based regimens. The choice of regimen should be based on patient characteristics, especially age, the results of viral drug resistance testing, drug efficacy and AEs, patient and family preference, pill size, and dosing frequency. Because adherence to the prescribed regimen is necessary, assessing patient and family preference should be weighed with this in mind.

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 superiority of a lopinavir/ritonavir (LPV/r)-based regimen compared to a nevirapine (NVP)-based regimen in infants and children aged 2 months to 35 months, regardless of prior 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 and 40.1% of children, respectively.¹

- Those in the NVP group demonstrated greater, but not statistically significant, improvements in CD4 counts and the participants’ 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 demonstrated in the NEVEREST study, where these parameters were compared in children who switched to a NVP regimen and those who continued on a LPV/r regimen after achieving virologic control.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 specific NNRTI or PI initiated). In the PI-based group, 49% of children received LPV/r and 48% received nelfinavir; in the NNRTI-based group, 61% of children received EFV and 38% received NVP. After 4 years of follow-up, 73% of children randomized to receive PI-based therapy and 70% 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 randomized to receive either an NNRTI- or LPV/r-based ART.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 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% CI, -9% to +17%).

Clinical investigation of INSTI-based regimens in children has been limited to noncomparative studies demonstrating safety, tolerability, and PKs. The recommendation for an INSTI as part of an initial regimen is based largely on extrapolation of efficacy from adult comparative trials that showed superior efficacy of INSTI-containing regimens compared to PI-containing and NNRTI-containing regimens⁷,⁸ and small studies in ART-naive adolescents.⁹

Based on the above data, the Panel considers the following as Preferred regimens for children when used in combination with two NRTIs:

- Aged <14 days: NVP or raltegravir (RAL)
- Aged ≥14 days to <3 years: LPV/r or RAL
- Aged ≥3 to <6 years: RAL, boosted atazanavir (ATV), or twice-daily boosted darunavir (DRV)
- Aged ≥6 to <12 years: Dolutegravir (DTG; for children weighing ≥30 kg) or boosted ATV
- Aged ≥12 years or body weight as noted for children who have not reached sexual maturity:
  - Weighing ≥30 kg: DTG
  - Weighing ≥35 kg: Elvitegravir/cobicistat (EVG/COBI; only the EVG/COBI-containing fixed-dose combination EVG/COBI/FTC/TAF is recommended at this time)
  - Weighing ≥40 kg: Boosted ATV or once-daily boosted DRV

Alternative regimens are shown in Table 7.

**Integrase Strand Transfer Inhibitor-Based Regimens**

Three INSTIs—DTG, EVG, and RAL—are licensed for the treatment of ARV-naive adults with HIV. These agents have quickly become the preferred regimen in adults because of their virologic efficacy, lack of drug-
drug interactions, and favorable toxicity profile. RAL is licensed for treatment of infants and children from birth. DTG is approved for use in children weighing ≥30 kg. EVG has been studied in adolescents in two fixed-dose combination regimens and in combination with two NRTIs and ritonavir (RTV) boosting. (Table 8 lists the advantages and disadvantages of INSTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.)

**Dolutegravir**

The FDA has approved DTG for use in children weighing ≥30 kg. The approval was supported by data from a study of 46 treatment-experienced (but INSTI-naive) adolescents and 11 treatment-experienced (but INSTI-naive) children aged ≥6 years. The drug has a very favorable safety profile and can be given once daily to treat INSTI-naive patients. Studies of this drug are ongoing in children as young as 4 weeks of age.

**Recommendation:**

- Based on the virologic potency and safety profile observed in adult and pediatric studies, the Panel recommends DTG in combination with a two-NRTI backbone as a Preferred INSTI regimen for children and adolescents weighing ≥30 kg (AI*).

**Elvitegravir**

EVG is an INSTI available as a tablet, a fixed-dose combination tablet containing EVG/COBI/FTC/TDF, and a fixed-dose combination tablet containing EVG/COBI/FTC/TAF. Both fixed-dose combinations are FDA-approved for use in ART-naive adults with HIV. EVG/COBI/FTC/TAF is FDA-approved for use in ART-naive children and adolescents weighing ≥25 kg. COBI is a specific, potent cytochrome P (CYP) 3A inhibitor that has no activity against HIV and is used as a PK enhancer, which allows for once-daily dosing of EVG.

**Recommendation:**

- Based on the virologic potency and safety profile observed in adult and adolescent studies, the Panel recommends EVG only in the fixed-dose combination EVG/COBI/FTC/TAF as a Preferred INSTI regimen for children and adolescents aged ≥12 years and weighing ≥35 kg who have creatinine clearances (CrCl) ≥30 mL/min (AI*).

- EVG/COBI/FTC/TAF is recommended as an Alternative INSTI regimen for children aged ≥6 years to 12 years and weighing ≥25 kg who have CrCl ≥30 mL/min (AI*).

**Raltegravir**

RAL is FDA-approved for treatment of infants and children weighing ≥2 kg and can be used starting at birth. It is available in film-coated tablets, chewable tablets, and single 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 the Antiretroviral Management of Newborns section.

**Recommendation:**

- Based on randomized clinical trials in adults and pediatric studies that were performed largely in ARV-experienced children and adolescents, the Panel recommends RAL as a Preferred INSTI in infants and children from birth to age <6 years. The Panel acknowledges that data regarding the efficacy of this agent in those aged <2 years are currently very limited.

- Although the current FDA label includes an increased dose of RAL that can be given once-daily, the Panel does not recommend once-daily dosing for initial therapy in children and infants at this time.

**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 an FDA-approved pediatric indication for
treatment of HIV infection. The advantages of NNRTIs as initial therapy include 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 compared to PIs. The major disadvantages of NNRTI drugs that are FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance (except ETR) and cross-resistance to other NNRTIs is common. Rare, but serious and potentially life-threatening, skin and hepatic toxicity can occur with all NNRTI drugs, but this AE is most frequently observed with NVP, at least in 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 NNRTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information for each drug.)

Efavirenz
EFV, when used in combination with two NRTIs, is an Alternative NNRTI for initial therapy in children aged ≥3 years to 12 years. This designation is based on clinical trial experience in adults and children. In children aged ≥3 months weighing ≥3.5 kg, EFV capsules can be opened and sprinkled on age-appropriate food.28 However, because of concerns regarding variable PK of the drug in very young patients, the Panel does not currently endorse its use for infants and children aged 3 months to 3 years.

Recommendation:
- Based on efficacy and tolerability,13,20,28-46 the Panel recommends EFV used in combination with a two-NRTI backbone as an Alternative NNRTI regimen for initial treatment of HIV in children aged ≥3 years (AI*).

Nevirapine
NVP has extensive clinical and safety experience in children with HIV and has shown ARV efficacy in a variety of combination regimens.1,5,6,47-51 NVP has also been used extensively as prophylaxis for the prevention of HIV transmission in young infants during the peripartum period and during breastfeeding. Although there is information about the safety and PKs of NVP when it is used at doses for prophylaxis that target lower NVP drug levels than those obtained with treatment doses, there is less information regarding the higher doses 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 NVP as a Preferred NNRTI if treatment initiation is planned 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 outcome compared to starting after age 14 days. Consultation with an expert in pediatric HIV infection should be sought. Additional considerations regarding the use of NVP in infants aged <14 days can be found in Antiretroviral Management of Newborns.

Recommendation:
- Based on the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare (but potentially life-threatening) instances of hepatitis,52,53 and conflicting data about virologic efficacy compared to preferred regimens,1,5,6,49-51,54-63 the Panel recommends NVP used in combination with a two-NRTI backbone as a Preferred NNRTI regimen in infants aged <14 days and an Alternative NNRTI regimen for children aged ≥14 days to <3 years (AI). A change from NVP to LPV/r should be considered after 14 days of life and 42 weeks post-gestational age based on infant genotype and the better outcomes of LPV/r in children aged <3 years.

Rilpivirine
RPV is currently available both as a single-agent formulation and a once-daily, fixed-dose combination tablet containing FTC and TDF. The single-agent formulation is approved for use in adolescents aged ≥12 years.

Recommendation:
- Based on the limited experience with RPV in adolescents and the larger body of evidence in adults,36,64-68 the Panel recommends RPV used in combination with a two-NRTI backbone as an Alternative NNRTI

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regimen for children and adolescents aged $\geq 12$ years and weighing $\geq 35$ kg who have HIV viral loads $\leq 100,000$ copies/mL (AI*).

**Protease Inhibitor-Based Regimens**

Advantages of PI-based regimens include excellent virologic potency and high barrier for development of drug resistance (since resistance requires multiple mutations). However, because PIs are metabolized via hepatic enzymes, the drugs have 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-naive 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), age of the child, and availability of data in children. (Table 8 lists the advantages and disadvantages of PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.)

RTV is a potent inhibitor of the CYP450 3A4 isoenzyme and can be used in low doses as a PK booster when co-administered 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. When RTV is used as a PI booster with other PIs, two agents must be administered. In addition, the use of RTV boosting increases the potential for hyperlipidemia and drug-drug interactions.

Preferred and alternative PIs are presented in alphabetical order below.

**Atazanavir/Ritonavir**

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 $\geq 6$ years. ATV is most often boosted with RTV (ATV/r). Approval was extended in 2014 for use in infants and children aged $\geq 3$ months and weighing $\geq 5$ kg. ATV in combination with COBI 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.

**Recommendation:**

- Based on virologic potency observed in adult and pediatric studies and tolerability seen in pediatric studies, the Panel recommends ATV/r used in combination with a two-NRTI backbone as a Preferred PI regimen for children aged $\geq 3$ years (AI*).

- Because of the limited experience with ATV/r in younger children, the Panel recommends ATV/r as Alternative PI therapy in infants and children aged $\geq 3$ months to $< 3$ years and weighing between 5 and 25 kg (AI*).

- The Panel does not recommend unboosted ATV.

**Darunavir/Ritonavir**

Darunavir/ritonavir (DRV/r) is FDA-approved for ARV-naive and ARV-experienced adults and for ARV-naive and ARV-experienced children aged $\geq 3$ years. DRV/r is approved for once-daily use in adults and children 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. 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. Because of the lack of efficacy data on once-daily DRV/r in treatment-naive or treatment-experienced children aged $< 12$ years, the Panel recommends dosing DRV/r twice daily in children aged $\geq 3$ years to $< 12$ years.

**Recommendation:**

- Based 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, the Panel recommends DRV/r used in combination with a two-NRTI backbone as a Preferred PI regimen for children aged ≥3 years to <6 years and children and adolescents aged ≥12 years (AI*).

- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of a Preferred PI regimen in treatment-naive children and adolescents weighing ≥40 kg (AI*).
- Twice-daily dosing of DRV/r is part of a Preferred PI regimen in children aged ≥3 to <6 years and weighing ≥10 kg and an Alternative PI regimen in children aged ≥6 years to <12 years (AI*).
- Twice-daily dosing of DRV/r should be used if the following DRV 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 for treatment of HIV infection in adults and in infants and children with a postmenstrual age ≥42 weeks and postnatal age ≥14 days. Once-daily LPV/r is FDA-approved for initial therapy in adults, but PK data in children do not support a recommendation for once-daily dosing.

**Recommendation:**
- Based on the virologic potency observed in adult and pediatric studies and the tolerability seen in pediatric studies, the Panel recommends LPV/r used in combination with a two-NRTI backbone as a Preferred PI regimen for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days to <3 years (AI).
- LPV/r, in combination with a two-NRTI backbone, is recommended as an Alternative PI regimen in children aged ≥3 years.

**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 FDA-approved for use in children aged <13 years. Dual-NRTI combinations that have been studied in children include: 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; and TAF used in combination with FTC. The Panel no longer recommends ddI or d4T as part of ARV regimens for children due to the significant toxicities observed with these drugs and the availability of safer agents. Advantages and disadvantages of different dual-NRTI backbone options recommended for initial therapy are delineated 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, 3TC and FTC are interchangeable. Both 3TC and FTC are well tolerated and have few AEs. Although there is less experience in children with FTC than with 3TC, 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 or 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 based on decreased viral fitness.

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

**Abacavir in Combination with Lamivudine or Emtricitabine**

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

- Based on virologic efficacy and favorable toxicity profile, the Panel recommends ABC plus 3TC or FTC as the Preferred dual-NRTI combination for children aged ≥3 months (AI).

- Once-daily dosing of ABC is recommended when using the pill formulation. Twice-daily dosing of liquid ABC is recommended for initial therapy; a change to once-daily dosing can be considered in clinically stable patients with undetectable viral loads and stable CD4 cell counts after approximately 6 months (24 weeks) of twice-daily dosing.

Tenofovir Alafenamide in Combination with Emtricitabine

TAF is an oral prodrug of tenofovir. It is approved by the FDA as a component of the fixed-dose combination 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 fixed-dose combination tablet. A fixed-dose combination that contains just FTC/TAF (Descovy) is also available.

Recommendation:

- Based on the potential for less renal and bone AEs with TAF when compared to TDF, the Panel recommends FTC/TAF as a Preferred dual-NRTI combination in children and adolescents aged ≥6 years who have estimated CrCl ≥30 mL/min when this combination is used as FTC/TAF with an INSTI or NNRTI. This combination is recommended as an Alternative drug combination when used in the single-tablet regimen EVG/COBI/FTC/TAF for children aged ≥6 years to <12 years and weighing ≥25 kg to <35 kg.

- For children and adolescents aged ≥12 years and weighing ≥35 kg, FTC/TAF is recommended as a Preferred drug combination when used in the single-tablet regimen EVG/COBI/FTC/TAF or as FTC/TAF used in combination with an NNRTI, INSTI, or a boosted PI.

- FTC/TAF is neither FDA approved 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.

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 licensed for treatment in infants aged ≥4 weeks and prophylaxis in newborns.

Recommendation:

- Because of the extensive experience and favorable safety profile, the Panel recommends ZDV used in combination with 3TC or FTC as a Preferred NRTI for infants and children from birth to age ≤6 years (AI*).

- In children aged ≥6 years and adolescents, the Panel recommends ZDV used in combination with 3TC or FTC as an Alternative NRTI because ZDV must be administered twice daily.

Alternative Dual-Nucleoside Reverse Transcriptase Inhibitor Regimens

Other dual-NRTI regimens have been studied in children, and the Panel recommends the following as alternative dual-NRTI combinations.

Tenofovir Disoproxil Fumarate in Combination with Lamivudine or Emtricitabine

TDF is FDA-approved 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. The potential risks of decreased BMD versus benefits of therapy should be considered.
Recommendation:
- Based on virologic efficacy and ease of dosing, the Panel recommends TDF used in combination with 3TC or FTC as an Alternative dual-NRTI combination for children aged ≥2 years to 12 years (AI*).

**Zidovudine in Combination with Abacavir and Zidovudine in Combination with Lamivudine or Emtricitabine**

ZDV plus ABC and ZDV plus 3TC had lower rates of viral suppression and more toxicity leading to drug modification than did ABC plus 3TC in a European pediatric study.94,101

Recommendation:
- The Panel recommends ZDV in combination with ABC as an Alternative dual-NRTI combination for use in children ≥3 months (BII).
- In children aged ≥6 years and adolescents who are not sexually mature (SMR 1–3), the Panel recommends ZDV used in combination with 3TC or FTC as an Alternative dual NRTI combination (BII).

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

An ART regimen for treatment-naive children generally contains one NNRTI or one PI boosted with RTV or COBI or one INSTI plus a two-NRTI backbone. Preferred regimens are designated based on efficacy, ease of administration, and acceptable toxicity. Alternative regimens have also demonstrated efficacy, but have more limited experience in children or less favorable ease of administration than Preferred regimens. Regimens should be individualized based on the advantages and disadvantages of each combination (see Table 8).

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

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Age</th>
<th>Regimens</th>
<th>Fixed-Dose Combination Available</th>
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<tbody>
<tr>
<td>Infants, Birth to Age &lt;14 Days</td>
<td>2 NRTIs plus NVP</td>
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<tr>
<td>Children Aged ≥14 Days to &lt;3 Years</td>
<td>2 NRTIs plus LPV/r</td>
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<td>Children Aged ≥3 Years to &lt;6 Years</td>
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<td>Children Aged ≥6 Years to &lt;12 Years</td>
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<td>Adolescents Aged ≥12 Years and SMR 1–3</td>
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<td>Adolescents Aged ≥12 Years and SMR 4 or 5</td>
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<table>
<thead>
<tr>
<th>Alternative Regimens</th>
<th>Age</th>
<th>Regimens</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥14 Days to &lt;3 Years</td>
<td>2 NRTIs plus NVP</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Children Aged ≥3 Months to &lt;3 Years and Weighing ≥10 kg</td>
<td>2 NRTIs plus ATV/r</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

<table>
<thead>
<tr>
<th>Age</th>
<th>Regimens</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥3 Years to &lt;6 Years</td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus LPV/r</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥6 Years to &lt;12 Years</td>
<td>2 NRTIs plus twice-daily DRV/r&lt;sup&gt;l&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus EVG/COBi&lt;sup&gt;l&lt;/sup&gt;</td>
<td>FDCs available</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus LPV/r</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 1–3</td>
<td>2 NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>2 NRTIs plus RPV&lt;sup&gt;i&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
</tbody>
</table>

**Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs**

<table>
<thead>
<tr>
<th>Age</th>
<th>2-NRTI Backbone Options</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, Birth to Age &lt;3 Months</td>
<td>ZDV plus (3TC or FTC)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥3 Months to &lt;6 Years</td>
<td>ABC plus (3TC or FTC)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>Children Aged ≥6 Years and SMR 1–3</td>
<td>ABC plus (3TC or FTC)&lt;sup&gt;k&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td></td>
<td>FTC/TAF&lt;sup&gt;f&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>Adolescents Aged ≥12 Years and SMR 4 or 5</td>
<td>Refer to the Adult and Adolescent Guidelines</td>
<td>No</td>
</tr>
</tbody>
</table>

**Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs**

<table>
<thead>
<tr>
<th>Age</th>
<th>2-NRTI Backbone Options</th>
<th>Fixed-Dose Combination Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Aged ≥3 Months</td>
<td>ZDV plus ABC</td>
<td>No</td>
</tr>
<tr>
<td>Children Aged ≥2 Years to 12 Years</td>
<td>TDF plus (3TC or FTC)&lt;sup&gt;m&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
<tr>
<td>Children and Adolescents Aged ≥6 Years and SMR 1–3</td>
<td>ZDV plus (3TC or FTC)&lt;sup&gt;n&lt;/sup&gt;</td>
<td>FDC available</td>
</tr>
</tbody>
</table>

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<sup>a</sup> 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. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Clinicians should consult an expert in pediatric HIV infection. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in Antiretroviral Management of Newborns. A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks 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), based on infant genotype and better outcomes of LPV/r than NVP in children aged <3 years. Data are very limited on the clinical outcomes of using RAL in infants and children aged <2 years.

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

<sup>c</sup> 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.

<sup>d</sup> DRV once daily should not be used in children aged <12 years or weighing <40 kg. DRV once daily should also not be used if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, L54L, L54M, T74P, L76V, L89V, and L89V. DRV/r is an Alternative recommendation for children aged ≥6 years to <12 years because there are options that can be administered once daily. It is Preferred for adolescents aged ≥12 years who are not sexually mature (SMR 1–3) where once-daily administration is possible.

<sup>e</sup> DTG is recommended only for children and adolescents weighing ≥30 kg. An FDC tablet containing ABC/DTG/3TC (Triumeq) is available.

<sup>f</sup> EVG is currently recommended only in FDC tablets. Tablets containing EVG/CObi/FTC/TAF are recommended as Preferred for children
Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, continued

and adolescents weighing ≥35 kg and as Alternative for children aged ≥6 years and weighing ≥25 kg.

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

* EFV is licensed for use in children aged ≥3 months and weighing ≥3.5 kg, but it is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years. An FDC tablet containing EFV/FTC/TDF (Atripla) is available.

* RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL. An FDC containing 3TC/ZDV (Combivir and generic) is available.

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

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

** Key to Acronyms:**
- **3TC** = lamivudine;
- **ABC** = abacavir;
- **ATV/r** = atazanavir/ritonavir;
- **ART** = antiretroviral therapy;
- **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;
- **NRTI** = nucleoside reverse transcriptase inhibitor;
- **NNRTI** = non-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

Figure 2. Preferred and Alternative Regimens by Age and Drug Class

<table>
<thead>
<tr>
<th>INI-based Regimens</th>
<th>Two NRTIs plus DTG&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two NRTIs plus EVF&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Two NRTIs plus RAL&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>NNRTI-based Regimens</td>
<td>Two NRTIs plus EFV&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Two NRTIs plus NVP&lt;sup&gt;6,g&lt;/sup&gt;</td>
<td>Two NRTIs plus RPV&lt;sup&gt;l&lt;/sup&gt;</td>
</tr>
<tr>
<td>Two NRTIs plus ATV/r&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Two NRTIs plus DRV/r&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Two NRTIs plus LPV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Two NRTIs plus LPV/r&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* 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, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Clinicians should consult an expert in pediatric HIV infection. Additional considerations regarding the use of NVP or RAL in infants aged <14 days can be found in Antiretroviral Management of Newborns. A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks post menstrual age (the span of time between the first day of the mother’s last menstrual period and birth, plus the time elapsed after birth), based on infant genotype and better outcomes of LPV/r than NVP in children aged <3 years. Data are...
very 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.

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.

c DRV once daily should not be used in children aged <12 years or weighing <40 kg. DRV once daily 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 an Alternative recommendation for children aged ≥6 years to <12 years because there are options that can be administered once daily. It is preferred for adolescents aged ≥12 years and SMR 1–3 where once-daily administration is possible.

d DTG is recommended only for children and adolescents weighing ≥30 kg. For those children weighing <30 kg, RAL can be considered if an INSTI-based regimen is desired.

EVG is currently recommended only in FDC tablets. Tablets containing EVG/Cobi/FTC/TAF are recommended as Preferred for children and adolescents weighing ≥35 kg and Alternative for children and adolescents weighing ≥25 kg.

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

EFV is licensed for use in children aged ≥3 months and weighing ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years.

RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

Key to Acronyms: ATV/r = atazanavir/ritonavir; 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; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide

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

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTIs In Alphabetical Order</td>
<td>All INSTIs</td>
<td>INSTI Class Advantages:  • Susceptibility of HIV to a new class of ARV drugs  • Few drug-drug interactions  • Well-tolerated</td>
<td>INSTI Class Disadvantages:  • Limited data on pediatric dosing or safety</td>
</tr>
<tr>
<td>DTG</td>
<td></td>
<td>Once-daily administration  • Can give with food  • Available in an FDC tablet containing ABC/DTG/3TC (Triumeq) in a single, but large, tablet  • Single-agent DTG pills are available in several dosages and are small in size.</td>
<td>Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing  • CNS side effects, particularly sleep disturbances</td>
</tr>
<tr>
<td>EVG</td>
<td></td>
<td>Once-daily administration  • Available in the following FDC tablets: EVG/Cobi/FTC/TDF (Stribild) and EVG/Cobi/FTC/TAF (Genvoya)</td>
<td>COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4).  • COBI inhibits tubular secretion of creatinine and may result in increased serum creatinine but normal glomerular clearance.</td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td>Can give with food  • Available in tablet, chewable tablet, and powder formulations  • Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥50 kg.</td>
<td>Potential for rare systemic allergic reaction or hepatitis  • Powder formulation requires a multistep preparation before administration.</td>
</tr>
</tbody>
</table>
Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children* (page 2 of 4)

<table>
<thead>
<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td>All NNRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>In Alphabetical Order</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI Class Advantages:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Long half-life</td>
<td></td>
<td>• Single mutation can confer resistance, with cross-resistance between EFV and NVP</td>
</tr>
<tr>
<td></td>
<td>• Less dyslipidemia and fat maldistribution than PIs</td>
<td></td>
<td>• Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP)</td>
</tr>
<tr>
<td></td>
<td>• PI-sparing</td>
<td></td>
<td>• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)</td>
</tr>
<tr>
<td></td>
<td>• Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NNRTI Class Disadvantages:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rash (generally mild)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• No commercially available liquid</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Limited data on dosing for children aged &lt;3 years</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• No data on dosing for children aged &lt;3 months</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>EFV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Once-daily administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Available in the FDC EFV/FTC/TDF (Atripla)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Potent ARV activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can give with food (but avoid high-fat meals)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Capsules can be opened and added to food</td>
<td></td>
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<td></td>
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<tr>
<td><strong>NVP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liquid formulation available</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dosing information for young infants available</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can give with food</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Extended-release formulation is available that allows for once-daily dosing in older children.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>PI Class Advantages:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• NNRTI-sparing</td>
<td></td>
<td>• Metabolic complications, including dyslipidemia, fat maldistribution, insulin resistance</td>
</tr>
<tr>
<td></td>
<td>• Clinical, virologic, and immunologic efficacy are well-documented.</td>
<td></td>
<td>• Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4)</td>
</tr>
<tr>
<td></td>
<td>• Resistance to PIs requires multiple mutations</td>
<td></td>
<td>• Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations</td>
</tr>
<tr>
<td></td>
<td>• When combined with a dual-NRTI backbone, a regimen containing a PI targets HIV at 2 steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.</td>
<td></td>
<td>• Poor palatability of liquid preparations, which may affect adherence to treatment regimen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Most PIs require RTV boosting, resulting in associated drug interactions.</td>
</tr>
<tr>
<td><strong>PI Class Disadvantages:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Should not use in patients with HIV viral load &gt;100,000 copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low barrier for resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children*

<table>
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<tr>
<th>ARV Class</th>
<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIs</strong>&lt;br&gt;In Alphabetical Order, continued</td>
<td><strong>Boosted ATV</strong>&lt;br&gt;• Once-daily dosing&lt;br&gt;• Powder formulation available&lt;br&gt;• ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).&lt;br&gt;• ATV requires a boosting agent. ATV/COBI is available as an FDC tablet (Evotaz), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of ATV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for ATV that is FDA-approved for use in children.</td>
<td>• No liquid formulation&lt;br&gt;• Food effect (should be administered with food)&lt;br&gt;• Indirect hyperbilirubinemia is common, but asymptomatic&lt;br&gt;• Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG)&lt;br&gt;• RTV component associated with a large number of drug interactions</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Boosted DRV</strong>&lt;br&gt;• Can be used once daily in children aged ≥12 years&lt;br&gt;• Liquid formulation available&lt;br&gt;• DRV requires a boosting agent. DRV/COBI is available as an FDC tablet (Prezenga), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of DRV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for DRV that is FDA-approved for use in children.</td>
<td>• Pediatric pill burden high with current tablet dose formulations&lt;br&gt;• Food effect (should be administered with food)&lt;br&gt;• Must be boosted to achieve adequate plasma concentrations&lt;br&gt;• Contains sulfonamide moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown.&lt;br&gt;• RTV component associated with a large number of drug interactions&lt;br&gt;• Can only be used once daily in the absence of certain PI-associated resistance mutations</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>LPV/r</strong>&lt;br&gt;• LPV only available coformulated with RTV in liquid and tablet formulations.&lt;br&gt;• Tablets can be given without regard to food, but may be better tolerated when taken with meal or snack.</td>
<td>• Poor palatability of liquid formulation (bitter taste), although palatability of combination is better than RTV alone&lt;br&gt;• Food effect (liquid formulation should be administered with food)&lt;br&gt;• RTV component is associated with large number of drug interactions&lt;br&gt;• 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&lt;br&gt;• Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)</td>
<td></td>
</tr>
<tr>
<td><strong>Dual-NRTI Backbones</strong>&lt;br&gt;In Alphabetical Order</td>
<td><strong>ABC plus (3TC or FTC)</strong>&lt;br&gt;• Palatable liquid formulations&lt;br&gt;• Can give with food.&lt;br&gt;• ABC and 3TC are available in the following FDC tablets: ABC/3TC (Epzicom and generic; for older/larger patients) and ABC/DTG/3TC (Triumeq; a single, large tablet).&lt;br&gt;• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>FTC/TAF for children aged ≥6 years</strong>&lt;br&gt;• Once-daily dosing&lt;br&gt;• Small tablet size&lt;br&gt;• Less TFV-associated renal and bone toxicity with TAF compared to TDF in adults&lt;br&gt;• FTC and TAF are available in the following FDC tablets: FTC/TAF (Descovy), EVG/COBI/FTC/TAF (Genvoya), and FTC/RPV/TAF (Odefsey).&lt;br&gt;• Limited data in children&lt;br&gt;• Increased lipids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children* (page 4 of 4)

<table>
<thead>
<tr>
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<th>ARV Agent(s)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual-NRTI Backbones In Alphabetical Order, continued</td>
<td>TDF plus (3TC or FTC) for adolescents with SMR 4 or 5</td>
<td>• Once-daily dosing for TDF • Resistance is slow to develop • Less mitochondrial toxicity than other NRTIs • Can give with food • Available as reduced-strength tablets and oral powder for use in younger children • FTC and TDF are available in the following FDC tablets: FTC/TDF (Truvada; available in multiple dosages), EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and FTC/RPV/TDF (Complera)</td>
<td>• Limited pediatric experience • Potential bone and renal toxicity; toxicity may be less in post-pubertal children • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV.</td>
</tr>
<tr>
<td></td>
<td>ZDV plus (3TC or FTC)</td>
<td>• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill (Combivir and generic) for older/larger patients. • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily.</td>
<td>• Bone marrow suppression with ZDV • Lipoatrophy with ZDV</td>
</tr>
<tr>
<td></td>
<td>ZDV plus ABC</td>
<td>• Palatable liquid formulations • Can give with food</td>
<td>• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment • Bone marrow suppression and lipoatrophy with ZDV</td>
</tr>
</tbody>
</table>

* See Appendix A: Pediatric Antiretroviral Drug Information and Table 7, Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios in the Adult and Adolescent Guidelines for more information.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV = atazanavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; CYP = cytochrome P; ddI = 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; PK = pharmacokinetic; 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

**References**


open-label, randomised phase 2/3 trial. 


46. Zagar A. Studies disagree on frequency of late cns side effects from efavirenz. AIDS Clin Care. 2006;4(1).


75. Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-
Conclusions: Darunavir plus ritonavir is noninferior to lopinavir/ritonavir in the treatment of HIV-1 infection in children. Darunavir/ritonavir is well tolerated and may have advantages over lopinavir/ritonavir in terms of pharmacokinetic properties, pharmacodynamics, and tolerability. Clinical trials in a broader range of populations and in different antiretroviral regimens are needed to further evaluate the use of darunavir/ritonavir in children.

References:


