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

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

Panel's Recommendations
• The selection of an initial antiretroviral (ARV) 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 8 below provides a list of Panel-recommended ARV 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 postpubertal 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 U.S. 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, as new therapies or drug formulations are developed, and as 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 when 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 below. Additional information regarding the advantages and disadvantages of specific drug combinations can be found in the What to Start: Initial Combination Antiretroviral Regimens for People With HIV 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, palatability problems, and the need to use multiple formulations to achieve an appropriate dose. 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, see the Hepatitis B Virus, Hepatitis C Virus, and Mycobacterium tuberculosis (TB) sections of the Pediatric Opportunistic Infection Guidelines.

Choosing an Initial Antiretroviral Regimen for Children With HIV

Preferred regimens for initial ARV 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 also should 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 International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 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 months 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 with 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 in 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 Nevirapine Resistance (NEVEREST) study, where these parameters were compared in children who were switched to an NVP-containing regimen and those who were continued on an LPV/r-containing regimen after achieving virologic suppression.[3] Improvements in metabolic parameters also have been seen in children who were 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 an 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,[5] 82% of children had viral loads <400 copies/mL.
- The PROMOTE pediatrics trial demonstrated comparable virologic efficacy among children who were randomized to receive either an NNRTI-based or an 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—which 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* initial regimens for children:

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

Preferred initial regimens by age, weight, and drug class are shown in Figure 1 below. Additional information about *Preferred* initial regimens, *Preferred* NRTI backbones, *Alternative* initial regimens, and *Alternative* NRTI backbones are shown in detail in Table 8 below.

Integrase Strand Transfer Inhibitor–Based Regimens

Four INSTIs—BIC, DTG, elvitegravir (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 due to 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 a weight of ≥2 kg. DTG is approved by the FDA for use in infants and children aged ≥4 weeks and weighing ≥3 kg. The FDC tablet BIC/FTC/TAF (Biktarvy) is approved by the FDA for use in children weighing ≥14 kg. EVG has been studied in adolescents in two FDC regimens and in combination with two NRTIs and ritonavir (RTV, r) 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 below 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. In October 2021, a lower strength formulation of BIC/FTC/TAF received FDA approval for use in children weighing ≥14 kg to <25 kg. BIC/FTC/TAF is approved for use in patients who are ART naive, and it also can 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 has been studied in adolescents (Cohort 1) aged 12 years to <18 years and weighing ≥35 kg and in two younger cohorts of children: Cohort 2, aged 6 years to <12 years and weighing ≥25 kg, and Cohort 3, aged ≥2 years and weighing ≥14 kg to <25 kg. All participants had maintained viral loads <50 copies/mL for ≥6 months. Cohorts 1 and 2 received the adult formulation of BIC/FTC/TAF. Children in Cohort 3 received BIC 30 mg/FTC 120 mg/TAF 15 mg. Overall, the drug was well tolerated in all participants in all cohorts. Drug exposure in all cohorts was similar to the exposure observed in adults. At 24 weeks, all 50 adolescents (Cohort 1) and 50 children (Cohort 2) maintained viral suppression, and at Week 48, 49 of 50 participants in each cohort maintained suppression.[14-15,16] Among children in Cohort 3, after 24 weeks, all 12 participants maintained viral suppression.[15,16]

Recommendation

- BIC/FTC/TAF is recommended as a *Preferred* INSTI-based regimen for children aged ≥2 years and weighing ≥14 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),[17,18] as well as a study of treatment-experienced (but INSTI-naive) older children.[9,19-21]

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.[7,9,17,18,21-23]
- Early concerns about the potential increased risk of NTDs with the use of DTG in women who were receiving DTG at the time of conception have decreased substantially. The Panel for Antiretroviral Guidelines for Adults and Adolescents and the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission include DTG among the preferred ARV agents for use in people of childbearing potential and for use by people who are pregnant or are trying to conceive. Pediatric and adolescent care providers should discuss risks and benefits with patients (and their caregivers) who are receiving or initiating DTG so that they can make informed decisions about the use of DTG (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers in the Perinatal Guidelines).

Elvitegravir

EVG is an INSTI that is available as a single-drug tablet, an FDC tablet that contains EVG/cobicistat (COBI, 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. 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 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. The Panel does not recommend EVG/c/FTC/TAF as a *Preferred* INSTI-based regimen because EVG has a lower barrier to resistance compared with BIC or DTG and the potential for multiple drug–drug interactions from COBI.[24-28]

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 due to 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.[7,29-37]
- Currently, the Panel **does not recommend** once-daily dosing of RAL for initial therapy in children and infants.

Non-Nucleoside Reverse Transcriptase Inhibitor–Based Regimens

Doravirine (DOR; for children weighing ≥35 kg), 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.

Doravirine

DOR is available both as a single-drug tablet and an FDC tablet that contains DOR 100 mg/3TC 300 mg/TDF 300 mg, marketed as Delstrigo. Efficacy studies in adults have demonstrated that DOR/3TC/TDF is noninferior to EFV-based regimens and darunavir (DRV)-based regimens. Virologic efficacy of DOR was similar in patients with higher viral loads >100,000 copies/mL as to those with viral loads ≤100,000 copies/mL. DOR, more so than EFV, compared favorably to the other drugs in these trials in terms of AEs (including better central nervous system tolerability) and is recommended as initial ART in adults with certain clinical situations. The FDC tablet has been studied in 45 adolescents aged 12 to 17 years and weighing ≥45 kg. Of these adolescents, 43 were virologically suppressed and two were ART naive. After 24 weeks of treatment, the regimen was well tolerated, with a low incidence of drug-related AEs (2.2%; 95% CI, 0.1–11.8). None of the AEs were serious or led to regimen discontinuation. HIV-1 RNA <50 copies/mL was demonstrated in all participants except for one ART-naive participant who met the criteria for virologic failure based on poor adherence to the study regimen.[38]

Recommendation

- DOR plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for initial treatment of HIV in children and adolescents weighing ≥35 kg **(BI*).** The Panel bases this recommendation on data from studies that evaluated the efficacy and tolerability of this drug in adults,[39-41] as well as early findings from pediatric PK studies.[38]

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 aged <3 years who have HIV and TB coinfection, because EFV is one of the few ARVs with minimal drug–drug interaction.[42]

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.[22,29,43-60]

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.[1,5,6,61-65] NVP also has been used extensively as prophylaxis for the prevention of HIV transmission in young infants during the peripartum period and during breastfeeding.[66] The safety and PKs of NVP have been studied at low doses used for prophylaxis. Less information is currently available from studies in very young infants about the safety and PKs of NVP at the higher doses required 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 before age 14 days. Although early treatment initiation may limit the size of the viral reservoir,[67,68]

no clinical trial data currently suggest that initiating treatment within the first 14 days of life improves outcomes compared to starting treatment after age 14 days (see When to Initiate Therapy in Antiretroviral-Naive Children). 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 as 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, 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.[1,5,6,63-65,69-76]

Rilpivirine

RPV is currently available both as a single-drug tablet and in once-daily FDC tablets. Three-drug FDC tablets containing FTC/RPV/TDF or FTC/RPV/TAF are approved for use in children and adolescents weighing ≥35 kg and aged ≥12 years.

RPV also is available as an extended-release injectable suspension in a kit that contains an extended-release injectable cabotegravir (CAB) suspension. The two-drug regimen of injectable CAB and RPV is not approved for initial ARV therapy but is FDA approved for use in adults and in children and adolescents aged ≥12 years and weighing ≥35 kg after they have obtained viral suppression on another regimen.

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.[50,77-80]

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[81] 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 atazanavir (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.[82,83] ATV administered in combination with COBI has been approved by the FDA for use in adults (using the single-agent COBI tablet) and in children weighing ≥35 kg.

Recommendation

- ATV/r plus a two-NRTI backbone is recommended as an *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.[32,46,79,81,84-89]
- 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 were switched back to the twice-daily regimen.[90] 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. Due to 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.[91] DRV administered in combination with COBI has been approved by the FDA for use in adults (using the single-agent COBI tablet) and in children weighing ≥40 kg.[92]

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.[32,93-100]
- Based on findings from the DIONE study, once-daily dosing of DRV/r can be used as 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,[101] but PK data in children do not support a recommendation for once-daily dosing.[102,103]

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.[22,48,84,85,93,101-108]

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. 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.[14,28,56,86,109-113]

See What Not to Start: Regimens Not Recommended for Use in Antiretroviral-Naive Children 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 zidovudine [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.[114,115]

The Panel no longer recommends using didanosine or stavudine as part of ARV regimens for children due to the significant toxicities observed when using these drugs and the availability of safer agents. These drugs are no longer commercially available for use in general.

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. ABC also has been reported to be safe in infants and children aged ≥1 month. More recently, an ABC dosing recommendation using PK simulation models has been endorsed by the World Health Organization using weight-band dosing for full-term infants from birth to 1 month of age. Based on this endorsement, the Panel recommends ABC from birth in full-term infants testing negative for the HLA-B5701 allele.[116,117]

Recommendation

- ABC plus 3TC or FTC is recommended as the *Preferred* dual-NRTI combination for children aged ≥3 months **(AI)** and for full-term infants from birth **(BIII).** A negative test for the HLA-B5701 allele should be obtained prior to starting ABC regardless of age.
- Studies of adults and children have reported virologic efficacy and favorable toxicity profiles for these combinations.[30,118-125] Recent data provide reassuring from the IMPAACT P1106 trial and two observational cohorts provide reassuring support for the safety of ABC use in infants when initiated at age <3 months.[126-128] Additional information about the use of ABC between birth and 1 month of age can be found in the Appendix A: Pediatric Antiretroviral Drug Information. Due to ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed before administration of ABC.
- 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.[129-132]

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.[27] TAF formulated as an FDC tablet with FTC and BIC is FDA approved for use in children weighing ≥14 kg (see Bictegravir).[14,133] An FDC tablet that contains FTC/TAF (Descovy) is available for use in children weighing ≥14 kg, with dosage determined by a child's weight. In January 2022, the FDA approved a lower strength formulation of the FTC/TAF FDC tablet for use in children weighing ≥14 kg to <25 kg.[134]

Coadministration of TAF with boosted ATV, DRV, or LPV increases 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 ≥14 kg with estimated CrCl ≥30 mL/min when used with an INSTI or NNRTI. FTC/TAF is 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*).** FTC/TAF also is recommended as a *Preferred* drug combination when used in the regimen BIC/FTC/TAF for children and adolescents weighing ≥14 kg **(AI*).** EVG/c/FTC/TAF is recommended as an *Alternative* drug regimen 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.
- 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.[110-113,135,136] Before starting treatment, clinicians should consider whether the benefits of using TDF outweigh the potential risk of decreased BMD.[137]

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.[110-113,119-122,138-143]

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 led to regimen modification than in patients who received ABC plus 3TC.[109,118] 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.[126-128]

Recommendation

- ZDV plus ABC is recommended as an *Alternative* dual-NRTI combination for children aged ≥1 month **(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 as an *Alternative* combination in children aged ≥1 month and adolescents **(AI*).** Twice-daily dosing is required for all ages with ZDV. Other NRTIs that require only once-daily dosing in children aged ≥6 years are available.[123,144-146]
- 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

	Patient Age and Weight Class				
	Birth to <14 Days of Age[a,b,c]	Aged ≥ 14 Days *and* ≥2 kg to <4 Weeks	Aged ≥4 Weeks *and* ≥3 kg to <2 Years	Aged ≥2 Years *and* ≥14 kg	Aged ≥6 Years *and* ≥25 kg
INSTI-Based Regimens	Two NRTIs plus RAL[c]				
				Two NRTIs plus BIC[d]	
			Two NRTIs plus DTG[e]		
NNRTI-Based Regimens	Two NRTIs plus NVP[a,f]				
PI-Based Regimens		Two NRTIs plus LPV/r[b]			

[a] Preferred NRTIs are listed in Table 8 below.

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. Although many pediatric experts favor initiating antiretroviral therapy as soon as possible after birth 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 than NVP in studies of children aged <3 years. 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 kg 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 kg.

[d] BIC is available only as part of a fixed-dose combination (FDC) tablet that contains BIC/FTC/TAF; this FDC tablet is recommended as a *Preferred* regimen for children aged ≥ 2 years and weighing ≥14 kg. Two strengths of BIC/FTC/TAF are available, with dosing according to a child's weight (see Bictegravir).

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

[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 tablets can be used in children weighing ≥14 kg. An FDC that contains ABC/DTG/3TC is available in dispersible tablets (Triumeq PD) for children weighing ≥10 kg to <25 kg and in a single tablet to be swallowed (Triumeq) for children weighing ≥25 kg. See Dolutegravir for information about dosing and administration.

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

Key: BIC = bictegravir; DTG = dolutegravir; 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 8. Antiretroviral Regimens Recommended for *Initial* Therapy for HIV Infection in Children

An antiretroviral (ARV) regimen for treatment-naive children is generally made up of a two–nucleoside reverse transcriptase inhibitor (NRTI) backbone and either one non-nucleoside reverse transcriptase inhibitor (NNRTI) **or** one integrase strand transfer inhibitor (INSTI) **or** one protease inhibitor (PI) boosted with ritonavir or cobicistat (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. Refer to Appendix A: Pediatric Antiretroviral Drug Information for additional information and recommended doses and formulations (also see Table 8 below). In addition, many drugs that are recommended for use in newborns 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.

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. Refer to the 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 at Time of Treatment Initiation			
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	≥3 kg	Two NRTIs plus DTG[d] Two NRTIs plus DTG[d]	No Yes (≥10 kg)
Children Aged ≥2 Years	≥14 kg	Two NRTIs plus BIC[e]	Yes

Table 8. Antiretroviral Regimens Recommended for *Initial* Therapy for HIV Infection in Children

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 Aged Birth to 1 Month	ABC plus (3TC or FTC)[f]	No[g]
	ZDV plus (3TC or FTC)[h]	No[g]
Infants and Children Aged >1 Month to <2 Years	ABC plus (3TC or FTC)[f]	Yes
Children and Adolescents Aged ≥2 Years With SMRs of 1–3	ABC plus (3TC or FTC)[f]	Yes
	FTC/TAF[i] in children and adolescents weighing ≥14 kg and receiving a regimen that contains an INSTI or an NNRTI FTC/TAF[i] in children and adolescents weighing ≥35 kg and receiving a regimen that contains a boosted PI	Yes
Adolescents Aged **≥12 Years** With SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines.	Yes

Alternative Regimens Based on Age and Weight at Time of Treatment Initiation			
Age	**Weight Restriction**	**Regimens**	**FDC Available**
Neonates, Infants, and Children **Aged ≥14 Days to <3 Years**	None	Two NRTIs plus NVP[j]	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[k]	No
	None	Two NRTIs plus EFV[l]	No[g]
	None	Two NRTIs plus LPV/r[b]	No
	≥25 kg	Two NRTIs plus EVG/c[m]	Yes
	≥35 kg	Two NRTIs plus DOR[n]	Yes
Adolescents Aged ≥12 Years With SMRs of 1–3	None	Two NRTIs plus ATV/r	No
	None	Two NRTIs plus DRV/r[k]	No
	None	Two NRTIs plus EFV[l]	Yes

Table 8. Antiretroviral Regimens Recommended for *Initial* Therapy for HIV Infection in Children

	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
	≥25 kg	Two NRTIs **plus** EVG/c[m]	Yes
	≥35 kg	Two NRTIs **plus** ATV/c[o]	No
		Two NRTIs **plus** DOR[n]	Yes
		Two NRTIs **plus** RPV[p]	Yes
	≥40 kg	Two NRTIs **plus** DRV/c[q]	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)[h]		No[g]
	ZDV **plus** ABC[f]		No
Children Aged ≥2 Years to 12 Years	TDF **plus** (3TC or FTC)[r]		Yes
Children and Adolescents Aged **≥6** Years and SMRs of 1–3	ZDV **plus** (3TC or FTC)[h]		Yes
	ZDV **plus** ABC[f]		No

[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. Although many pediatric experts favor initiating antiretroviral therapy as soon as possible after birth 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 than NVP in studies of children aged <3 years. 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). Some experts would choose not to start with LPV/r as a *Preferred* initial regimen in neonates aged ≥14 days to <4 weeks but would choose to start with NVP instead.

[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 kg 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 and administered to infants as young as 4 weeks of age who weigh at least 3 kg.

[d] 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 tablets can be used in children weighing ≥14 kg. An FDC that contains ABC/DTG/3TC is available in dispersible tablets (Triumeq PD) for children weighing ≥10 kg to <25 kg and in a single tablet to be swallowed (Triumeq) for children weighing ≥25 kg. See Dolutegravir for information about dosing and administration.

[e] 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 ≥14 kg. Two strengths of BIC/FTC/TAF are available, with dosing according to a child's weight (see Bictegravir).

Table 8. Antiretroviral Regimens Recommended for *Initial* Therapy for HIV Infection in Children

[f] ABC is not approved by the U.S. Food and Drug Administration (FDA) for use in full-term neonates and infants aged <3 months. Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on the safety of ABC in infants when initiated at the age of <3 months (see Abacavir). Before ABC administration, a negative HLA-B 5701 allele test should be available. An FDC tablet that contains ABC/3TC (Epzicom and generic) is available for use in children weighing ≥25 kg.

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

[h] An FDC tablet that contains 3TC/ZDV (Combivir and generic) is available for use in children weighing ≥30 kg. Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) prefer ABC over ZDV because ABC can be dosed once daily.

[i] FTC plus TAF is recommended as a *Preferred* NRTI combination for children and adolescents weighing ≥14 kg when used with an INSTI or NNRTI; an FDC tablet that contains FTC/TAF (Descovy) is available in two strengths, with dosage determined by a child's weight (see Tenofovir Alafenamide). FTC/TAF is approved by the FDA for children weighing ≥14 kg when used in the regimen BIC/FTC/TAF, which is also available in two strengths, with dosage determined by a child's weight. EVG/c/FTC/TAF is approved for use in children weighing ≥25 kg. FTC/TAF is a *Preferred* NRTI combination for children and adolescents weighing ≥35 kg when used with a boosted PI; FTC/TAF is not approved or recommended for use with a boosted PI in children weighing <35 kg.

[j] NVP should not be used in post-pubertal girls with T lymphocyte cell 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.

[k] 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).

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

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

[n] DOR is not FDA approved for pediatric use. Based on data from studies that evaluated the efficacy and tolerability of DOR in adults, as well as early findings from pediatric PK studies, the Panel recommends DOR as an *Alternative* ARV for children and adolescents weighing ≥35 kg. An FDC tablet containing DOR/3TC/TDF is available.

[o] ATV/c is available as an FDC tablet containing ATV/c (Evotaz) that has been approved by the FDA for use in children and adolescents weighing ≥35 kg.

[p] 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.

[q] 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.

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

Key: 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; 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; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for *Initial* Therapy in Children

See Appendix A: Pediatric Antiretroviral Drug Information and Table 8. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios in the Adult and Adolescent Antiretroviral Guidelines for more information.

ARV Class/ Agent(s)	Advantages	Disadvantages
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. Antiretrovirals Available in Fixed-Dose Combination Tablets)	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. Antiretrovirals Available in Fixed-Dose Combination Tablets) Single-agent DTG pills are available in several doses and are small in size. DTG and the FDC ABC/DTG/3TC are 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 Early concerns about a possible increased risk of NTDs in infants born to women who were receiving DTG at the time of conception have decreased substantially. The Panel for Antiretroviral Guidelines for Adults and Adolescents and the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission include DTG among the preferred ARV agents for use in people of childbearing potential and for use in people who are pregnant or are trying to conceive. Risks and benefits should be discussed to support informed decision-making (see Dolutegravir, Appendix C: Antiretroviral Counseling Guide for Health Care Providers).
EVG	Once-daily administration Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	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	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.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for *Initial* Therapy in Children

ARV Class/ Agent(s)	Advantages	Disadvantages
	Chewable tablets can be crushed and mixed with various liquids for infants ≥4 weeks of age who weigh ≥3 kg. Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥40 kg.	
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; these toxic effects have not been reported in neonates. • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4). Information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.
DOR	Once-daily administration Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets) Can be taken with or without food Has continued antiviral activity in the setting of some NNRTI mutations	Neuropsychiatric AEs, but fewer than reported for EFV DOR is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers (see Doravirine). Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours after a fixed-dose combination of DOR/3TC/TDF or an increase of the DOR dose to 100 mg twice daily (see Doravirine).
EFV	Once-daily administration Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets) 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	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

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for *Initial* Therapy in Children

ARV Class/ Agent(s)	Advantages	Disadvantages
	Extended-release formulation that allows once-daily dosing in older children is available.	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. Antiretrovirals Available in Fixed-Dose Combination Tablets)	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
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.
Boosted ATV	Once-daily dosing Powder formulation is available. ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	No liquid formulation Should be administered with food Indirect hyperbilirubinemia is common, but asymptomatic. Scleral icterus may be distressing to the patient, which may affect adherence. Must be used with caution in patients with preexisting conduction system defects (can prolong the PR interval of an 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.	Pediatric pill burden high with current tablet dose formulations Should be administered with food Must be boosted to achieve adequate plasma concentrations

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for *Initial* Therapy in Children

ARV Class/ Agent(s)	Advantages	Disadvantages
	Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	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 be used only once daily in the absence of certain PI-associated resistance mutations.
LPV/r	LPV is only available coformulated with RTV in liquid and tablet formulations. Tablets can be given without food, but they may be better tolerated when taken with a 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 an ECG)
ABC plus (3TC or FTC)	Palatable liquid formulations Can give with food Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	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. Antiretrovirals Available in Fixed-Dose Combination Tablets)	Limited data on the safety and efficacy of this combination in children Increased lipid levels
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	Limited pediatric experience Potential bone and renal toxicity Appropriate dosing is complicated by numerous drug–drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for *Initial* Therapy in Children

ARV Class/ Agent(s)	Advantages	Disadvantages
	Available as reduced-strength tablets and oral powder for use in younger children Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	
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 requires twice-daily dosing.
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 ZDV requires twice-daily dosing.

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; DOR = doravirine; 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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