WHAT TO START: ANTIRETROVIRAL TREATMENT REGIMENS RECOMMENDED FOR INITIAL THERAPY IN INFANTS AND CHILDREN WITH HIV

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Panel's Recommendations
• The selection of an initial antiretroviral regimen for the treatment of HIV in infants and children should be individualized based on factors that include patient characteristics (e.g., age, weight), regimen characteristics (e.g., efficacy, safety, tolerability), clinical and practical considerations, patient and family preferences, and the results of HIV resistance testing **(AIII)** (see Table A below and Appendix A. Pediatric Antiretroviral Drug Information). • For infants and children initiating treatment for HIV for the first time, the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV recommends initiating antiretroviral therapy (ART) with three drugs: a dual–nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone plus an integrase strand transfer inhibitor anchor drug, when possible. In some circumstances, an ART regimen of two NRTIs plus a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor as the anchor drug may be indicated for initial treatment **(AI*).** See Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy in Infants and Children With HIV below.
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) regimens have directly compared different treatment regimens in pediatric patients. 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 viral load (plasma HIV RNA concentration) and CD4 T lymphocyte (CD4) cell count. The Panel 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 antiretroviral (ARV) 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. However, if pediatric data are lacking, evidence in adolescents and adults is considered.
- 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 ease of administration, formulation options (e.g., syrups, powders, or granules vs. chewable tablets vs. pediatric dispersible tablets), palatability, pill size, and number of pills or volume of oral solution needed for an appropriate dose.
- Dosing frequency and food and/or fluid requirements.
- The potential for drug interactions with other medications.

ART regimens recommended for use in children with HIV should generally consist of a backbone of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus a third active anchor drug from one of the following classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a PK enhancer (also known as a booster; the two drugs used for this purpose are cobicistat [COBI or c] and ritonavir [RTV or r]).

The Panel classifies recommended ARV drugs or ART regimens for **initial** treatment of HIV in infants and children into one of two categories:

- *Preferred:* ARV drugs or drug combinations are designated as *Preferred* for initial ART in infants and children without ART experience when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy and when pediatric studies using surrogate markers have demonstrated safety and appropriate drug exposure. Age and weight requirements, formulations, dosing frequency, potential drug interactions, and other factors are also considered when designating ARV drugs or ART regimens as *Preferred*.
- *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 initial ART regimens in children if they are less effective or durable than a *Preferred* regimen in children or adults; 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.

ARV drugs or regimens that are not recommended for initial ART in children are discussed in the What Not to Start: Regimens Not Recommended for Initial Antiretroviral Therapy in Infants and Children below. For detailed pediatric information on each drug, see Appendix A. Pediatric Antiretroviral Drug Information.

Factors to Consider When Selecting an Initial Antiretroviral Therapy Regimen

ART regimens for infants and children should contain three fully active drugs for durable and potent virologic suppression. When possible, the initial treatment should reflect an option that requires only

once-daily dosing and minimizes the number of liquid formulations, dispersible tablets, or pills that must be administered. Therefore, Panel recommendations reflect once-daily ARV regimens and single-tablet regimens whenever feasible.

Panel recommendations about ARV drugs and drug combinations for initial ART regimens in infants and children are influenced by the availability of FDA-approved drugs. FDA drug approvals of pediatric formulations and approvals for the use of adult formulations in children are based on weight but include age limitations for some drugs. Although age can be used as an initial guide when selecting ARV drugs for use in infants and children, body weight is the preferred determinant for drug selection and drug dosing in infants and children. Gestational age at birth and postnatal age must also be considered in the selection of some drugs for infants. Many drugs that are recommended for use in young infants do not have dosing recommendations for infants born prior to 37 weeks of gestational age (i.e., born preterm).

When making recommendations, the Panel considers efficacy and factors affecting the efficacy of a regimen, age and weight requirements, potential toxicity, tolerability, and drug or regimen characteristics that affect administration and adherence (e.g., formulations, pill size, dosing frequency). Table A below summarizes factors to consider when selecting an ART regimen for infants and children. Details about ARV formulations, fixed-dose combinations, dosing, and administration to infants and children are provided in Appendix A. Pediatric Antiretroviral Drug Information. Advantages and disadvantages of ARV components recommended for initial therapy in infants and children are summarized in Table B and Table 9 below. Additional information is provided in the Adult and Adolescent Antiretroviral Guidelines.

The Panel recommends rapid initiation of ART (defined as initiating ART immediately or within days of diagnosis), accompanied by a discussion about the importance of adherence and provision of adherence support for all children with HIV (see When to Initiate Antiretroviral Treatment in Children With HIV Infection and Adherence to Antiretroviral Therapy in Children and Adolescents With HIV).

Table A. Factors to Consider When Selecting an Antiretroviral Treatment Regimen for Children

Factors to Consider	Key Questions and Comments
Acquired potential drug resistance	Are there any concerns that the child[a] may have HIV virus resistant to certain ARV drugs?
Age and weight	Are dosing, PK, and safety information for an ARV drug available based on the child's weight and age? Are there weight and/or age requirements for ARV drug use per FDA approvals or Panel recommendations, including gestational age and postnatal age requirements? Do efficacy and safety data support the choice of specific ARV drugs as part of an initial ART regimen? Is weight-band dosing information available? Weight-band dosing minimizes the need for frequent dose adjustments.
Available formulations	What drug formulations are available for potential treatment regimens (e.g., liquids, dispersible tablets, film-coated tablets that must be swallowed whole, tablets that can be crushed or split)? If pills are available, what is the pill size?

Table A. Factors to Consider When Selecting an Antiretroviral Treatment Regimen for Children

Factors to Consider	Key Questions and Comments
	Are multiclass single-tablet regimens available? See Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class and Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.
Frequency of dosing	Is a once-daily regimen possible?
Preparation and administration of medication by caregivers	How complicated is preparing the medication(s) needed for the ART regimen? What can be done to ensure that caregivers can safely and accurately administer the medications? Providers should complete the following: • Provide medication counseling with trained medical staff. • Provide correctly sized oral syringes. • For liquids, ensure that bottles include stoppers to minimize spilling and medication wastage. • Provide medication calendars after discussing who will be administering the ART and identifying the most convenient time for administration. • Address any food restrictions or requirements for ARVs to be given with food. • Repeat teaching at each clinic visit.
Palatability and tolerance	How palatable and well-tolerated is the regimen?
Ability to swallow pills	Can this child swallow pills or be taught how to swallow pills? The age that a child can learn the skill of swallowing pills varies. Usually, children aged 4 years and older can be taught to swallow pills.
Drug–drug interactions	Does the child require chronic treatment for any other conditions (e.g., mental health conditions, seizure disorders, tuberculosis)? If so, are there any potential drug interactions? See Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.
Contraindications	Are there contraindications to prescribing a specific ARV or ART regimen? For example, a positive HLA-B*5701 allele test result is a contraindication for use of abacavir.
Comorbidities and pregnancy	Are there other factors that can affect ARV choices for the drug regimen? Examples include tuberculosis, hepatitis B virus infection, and, for adolescents, pregnancy.
Toxicity	What are the most common side effects and safety profiles for the ARV drugs? See Appendix A. Pediatric Antiretroviral Drug Information. Are there specific toxicity or side effect considerations for individual children (e.g., weight gain in children or adolescents who are overweight or obese, depression)?

Table A. Factors to Consider When Selecting an Antiretroviral Treatment Regimen for Children

Factors to Consider	Key Questions and Comments
Availability,[b] cost, and insurance coverage	Are the medications and formulations needed readily available? Some new drugs or pediatric formulations may not be available in certain areas, or concerns may exist about maintaining a continuous supply. Does the child have insurance coverage? Can the family afford out-of-pocket costs (e.g., co-pays)? Does the regimen require prior authorization?

[a] For the sake of brevity, the term "child" encompasses infants, children, and prepubertal adolescents.

[b] Because some ARV medications or pediatric formulations may not be available in certain hospitals or geographic areas, clinicians should check availability and advocate for additions to formularies at local hospitals and/or pharmacies as needed.

Key: ART = antiretroviral therapy; ARV = antiretroviral; FDA = U.S. Food and Drug Administration; HLA = human leukocyte antigen; PK = pharmacokinetic; the Panel = the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV

Panel Recommendations for Initial Antiretroviral Therapy Regimens in Infants and Children

The following subsections group Panel recommendations for initial ART regimens for children, including prepubertal adolescents, with HIV infection according to a child's age (birth to <30 days, ≥30 days to <2 years, ≥2 years to <12 years, and ≥12 years). These guidelines provide recommendations for prepubertal children and adolescents (i.e., those with sexual maturity ratings [SMR] of 1 to 3).[1] The Adult and Adolescent Guidelines address recommendations for postpubertal adolescents (i.e., those with an SMR of 4 and 5); see What to Start. It is important to point out that pediatric approvals for most drugs are now based on specific weight parameters and that weight, rather than SMR, is a key determinant in ARV drug selection.

Preferred regimen for initial ART in full term infants aged <30 days with HIV-1 infection include an NRTI backbone of two NRTIs plus an INSTI (dolutegravir [DTG]) as the anchor drug for term newborns ≥37 weeks of gestation. INSTI-based regimens (INSTI plus two NRTIs) are *Preferred* for initial ART in infants and children aged ≥30 days with HIV-1 infection whenever possible. ***Preferred* anchor drugs,** by age and weight, are listed below with *Alternative* options discussed in subsections by age group:

- Full-term newborns and infants aged <30 days (gestational age ≥37 weeks): DTG if weight ≥2 kg; see Table 8 below regarding gestational age considerations.
- Infants and children aged ≥30 days: 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 (FTC)/tenofovir alafenamide (TAF).

INSTI-based regimens have become the *Preferred* option for initial ART regimens in infants and children (and adults) whenever possible due to their virologic efficacy, lack of drug interactions, and favorable toxicity profile.[2-5] This pediatric recommendation is consistent with recommendations for initial ART in adults and adolescents (see the What to Start: Initial Combination Antiretroviral Regimens for People With HIV section of the Adult and Adolescent Antiretroviral Guidelines). Adult comparative trials have shown that INSTI-containing regimens have superior efficacy compared with

PI-containing and NNRTI-containing regimens,[6,7] and an increasing number of studies have evaluated the PK, safety, tolerability, and efficacy of these drugs in infants, children, and adolescents (see the Raltegravir, Dolutegravir, and Bictegravir sections).

Raltegravir (RAL) is a first-generation INSTI and is the only INSTI option currently approved by the FDA for use in infants aged <30 days. INSTI-based regimens using second-generation INSTIs that have greater efficacy and a higher barrier to resistance than RAL (i.e., **DTG** or **BIC** depending on age and weight) are recommended for initial therapy in children. Recent data support the use of DTG beginning at birth in full term neonates ≥2 kg.[8-10]

Planning for Transitions in Antiretroviral Therapy Regimens

When initiating treatment in infants and children, it is recognized that there may be more potent drug options, options with lower administration burden on a caregiver, and options with lower liquid volume requirements or pill burden as an infant or child gains weight or increases in age and develops the ability to swallow pills. This section briefly addresses planning regimen transitions. Information and recommendations about the sequence and selection of ARV drugs after initial therapy are provided in other Guidelines sections. Modifying Antiretroviral Regimens in Children With Sustained Viral Suppression on Antiretroviral Therapy discusses modifications to simplify or optimize treatment or to manage a specific toxicity. Recognizing and Managing Antiretroviral Treatment Failure discusses situations where viral suppression has not been reached on initial ARV therapy. Management of Medication Toxicity or Intolerance provides an overview of management with links to toxicity tables (e.g., Lipodystrophies and Weight Gain, Dyslipidemia) that address specific issues.

Selection of Dual–Nucleoside Reverse Transcriptase Inhibitor Backbone as Part of Initial Antiretroviral Therapy Regimens

Dual-NRTI combinations form the backbone of ART regimens for HIV treatment in both adults and children and are used in combination with an anchor drug from one of the following ARV classes: INSTIs, PIs, or NNRTIs. Dual-NRTI backbones recommended by the Panel as part of *Preferred* or *Alternative* ART regimens for children or for use in special circumstances are listed below, with links to sections in Appendix A. Pediatric Antiretroviral Drug Information that provide detailed information about the formulations, dosing, safety, and use of each drug in infants and children.

- (Zidovudine [ZDV] or abacavir [ABC]) plus (lamivudine [3TC] or FTC)
- TAF plus FTC for children weighing ≥14 kg. Some FDCs for complete ART regimens that include TAF have varying weight and age requirements.
- Tenofovir disoproxil fumarate (TDF) plus 3TC or FTC for children aged ≥2 years and weighing ≥10 kg

Dual-NRTI selection is influenced by a child's weight and age, as well as the availability of FDCs for NRTI combinations or FDCs for complete ART regimens. The advantages and disadvantages of the different dual-NRTI backbone options that are recommended for initial therapy in children are shown in Table 9 and discussed briefly below.

ZDV has been shown to be safe and effective as part of an ART regimen for infants and children. However, hematologic toxicity (anemia, neutropenia)[11-15] and twice-daily dosing of ZDV—a requirement for all ages—limit the long-term use of ZDV in children.

ABC is approved by the FDA only for use in children aged ≥3 months, but the Panel recommends use of ABC from birth in full-term infants (see Abacavir).[16-18] A negative test for the human leukocyte antigen (HLA)-B*5701 allele must be obtained prior to use of ABC. HLA screening reduces the risk of ABC-associated hypersensitivity reaction: In a double-blind randomized study, 3.4% incidence of hypersensitivity reaction was diagnosed in the prospective HLA screening group versus 7.8% in the control group.[19] The prevalence of the HLA-B*5701 allele varies globally. In a predominantly white population (~83%) the prevalence is 5.6%, while the prevalence of this genotype in West Africa (including Burkina Faso) and Central Africa (including Uganda) is reported to be very low, at 0.1% in one study[20] and 0.2% in another.[21]

3TC and FTC are considered interchangeable as part of ART regimens; both are well tolerated and are associated with few adverse effects (AEs). FTC can be substituted for 3TC as one component of a *Preferred* dual-NRTI backbone (i.e., FTC plus ABC, TDF, or ZDV). 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 (see Stanford HIV Drug Resistance Database).

TDF is approved for use in children at least 2 years of age. It is available as a stand-alone drug in both powder or tablet formulations and is also contained in multiple FDC products. TDF administration is associated with decreased bone mineral density (BMD) and disruption of vitamin D metabolism in both adults and children.[22,23] Vitamin D supplementation is recommended for people receiving a TDF-containing regimen who are identified as having vitamin D deficiency (see Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis). New onset renal impairment and worsening renal impairment have been reported in both adults and children receiving TDF. Although TDF is associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.[24,25] Irreversible renal failure is very rare, but cases have been reported.[26] With long-term use of TDF, renal toxicity can occur at the site of the proximal convoluted tubules, with clinical manifestations ranging from asymptomatic proteinuria to progressively declining glomerular filtration rates.[24,27,28] The combination of TDF with atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or lopinavir/ritonavir (LPV/r) increases plasma tenofovir (TFV) concentrations and the risk of TDF-associated toxicity.[29]

TAF is available only in FDC tablets that must be swallowed whole. With TAF, the active drug TFV achieves higher intracellular concentrations and lower plasma concentrations than TDF. Bone and renal toxicity associated with TDF is linked to higher plasma concentrations of TFV, which may explain why these toxicities occur less frequently with TAF. Use of COBI- or RTV-boosted PIs in combination with TAF/FTC is not recommended in children weighing <35 kg because these drugs can increase TAF exposure, and no data are available on the use of these combinations. In children and adolescents weighing ≥35 kg, boosted PIs can be used with TAF/FTC.

Weight gain and increased risk for clinical obesity have been reported in adults with the use of TAF- and INSTI-containing regimens,[30,31] but these side effects have not been clearly demonstrated in children.[32-34] Furthermore, use of TAF-containing regimens has also been associated with increased levels of total and low-density lipoprotein cholesterol and triglycerides. When these concerns arise, regimens containing TDF may be preferable. However, providers must consider the risks of proximal renal tubular injury, rare irreversible renal failure, and decreased BMD that can occur when TDF is used. Since TAF is associated with less bone and renal toxicity than TDF but has equal antiviral efficacy, TAF is preferred over TDF for most pediatric patients.

Nucleoside Reverse Transcriptase Inhibitor Backbone Selection With Hepatitis B Virus Coinfection

When selecting the NRTI backbone for an initial ART regimen, FTC, 3TC, TDF, and 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* sections of the Pediatric Opportunistic Infection Guidelines.

Recommended Initial Antiretroviral Therapy Regimens for Infants From Birth to <30 Days of Age

Panel recommendations for the anchor drugs for *Preferred* and *Alternative* initial ART regimens in infants aged <30 days (i.e., DTG, RAL, nevirapine [NVP], and LPV/r) is dependent on gestational age at birth, the infant's postmenstrual age (calculated as gestational age at birth plus postnatal age), and current weight at the time the ARV regimen or specific ARV drug is initiated.[35]

Preferred Regimens

- Term infants (≥37 weeks gestation) or preterm infants with a postmenstrual age ≥37 weeks at the time of treatment initiation:
  - DTG (for infants weighing ≥2 kg) plus ZDV plus (3TC or FTC) ***or***
  - NVP (for infants weighing <2 kg) plus ZDV plus (3TC or FTC)
- Preterm infants with a postmenstrual age ≥32 weeks to <37 weeks at the time of treatment initiation:
  - NVP plus ZDV plus (3TC or FTC)
- Preterm infants with a postmenstrual age <32 weeks at the time of treatment initiation:
  - Consultation with a pediatric HIV expert or the National Perinatal HIV/AIDS Hotline (1-888-448-8765) is recommended.

Rationale

The Panel recommends DTG administered with an NRTI backbone of ZDV plus 3TC or FTC as an initial regimen for the treatment of HIV-1 infection in infants born at ≥37 weeks and weighing ≥2 kg.[36-42] NVP administered with an NRTI backbone of ZDV plus 3TC or FTC is *Preferred* as an initial regimen for preterm infants or term infants weighing <2 kg. The selection of anchor drug and regimen will depend on several factors, such as ARV resistance during pregnancy, the infant's gestational age at birth, current postmenstrual age, weight at treatment initiation, the caregiver's perceived ease of preparing and dosing, availability of appropriate formulations, and availability of medications in the outpatient setting. These factors have been summarized below in Table B. Advantages and Disadvantages of ARVs Recommended for Initial Antiretroviral Therapy in Infants From Birth to <30 Days of Age. HIV resistance testing and HLA-B*5701 should be included in the initial workup for all infants and children with HIV at the time of HIV diagnosis and before initiation of ART but should not delay treatment initiation. Initial ART regimens can be modified if needed based on drug resistance testing results (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

At the time of HIV diagnosis, some infants at high risk for HIV acquisition may have initiated presumptive HIV therapy. The regimens recommended for presumptive HIV therapy are addressed in Antiretroviral Management of Infants With *In Utero*, Intrapartum, or Breastfeeding Exposure to HIV and are the same as the ARV regimens recommended for treatment of HIV in neonates. Therefore, once the diagnosis of HIV-1 is established in the neonate, the regimen for presumptive HIV therapy can be continued—now as definitive ART—with virologic monitoring to establish successful viral suppression (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

At the time of HIV diagnosis, some infants at low risk for HIV acquisition might be receiving ZDV alone as prophylaxis. If the infant has a positive HIV nucleic acid test, a complete ART regimen should be initiated without waiting for the results of a confirmatory test. In this case, ZDV may be continued with the addition of a second NRTI and DTG as long as the infant's postmenstrual age is ≥37 weeks and weight is ≥2 kg. *Alternative* regimens including RAL, NVP, or an LPV/r-based regimen appropriate for the infant's age and weight can be used (see *Alternative* Regimens below). If confirmatory testing indicates the infant does not have HIV, ART can be discontinued.

Alternative Regimens

Alternative Anchor Drug

RAL (for infants weighing ≥2 kg) plus ZDV plus (3TC or FTC):

The Panel recommends RAL in combination with the NRTI backbone recommended in *Preferred* Regimens above as an *Alternative* anchor drug for infants. Although RAL is the only INSTI currently approved by the FDA for use in neonates, it has a lower barrier to viral resistance than DTG, involves a multistep process for preparation, and has a complicated dosing schedule for the first few weeks of life.[43-45] There is extensive experience with RAL in full-term neonates.

NVP plus ZDV plus (3TC or FTC):

The Panel continues to recommend NVP in combination with the NRTI backbone recommended in *Preferred* Regimens above as a *Preferred* drug for preterm infants and as an *Alternative* for full-term infants ≥2 kg; for infants weighing <2 kg, NVP continues to be a *Preferred* anchor drug. There is extensive data on the efficacy and safety of NVP in children. Infants with a postmenstrual age ≥42 weeks *and* a postnatal age of ≥14 days:

LPV/r plus ZDV plus (3TC or FTC):

The Panel recommends LPV/r oral solution in combination with the NRTI backbone recommended in *Preferred* Regimens above as an *Alternative* anchor drug for infants with a postmenstrual age of ≥42 weeks of gestation and a postnatal age of ≥14 days. LPV/r oral solution contains 42.4% (volume/volume) alcohol and 15.3% (weight/volume) propylene glycol. Use of this drug in infants before 42 weeks postmenstrual age and before a postnatal age of 14 days, when hepatic metabolic function and kidney excretory function are maturing, can lead to accumulation of LPV, alcohol, and propylene glycol, resulting in serious cardiac, renal, metabolic, or respiratory problems. For more information about LPV/r use in newborns, refer to the Lopinavir/Ritonavir section in Appendix A. Pediatric Antiretroviral Drug Information.

Alternative Nucleoside Reverse Transcriptase Inhibitor Backbone

- Term infants (≥37 weeks gestation):
  - ABC plus (3TC or FTC) if HLA-B*5701 negative

ABC: A negative test for the HLA-B*5701 allele must be obtained prior to use of ABC. Although ABC is not FDA approved for use in infants aged <3 months, the Panel recommends ABC as part of an *Alternative* NRTI backbone for full-term infants from birth (see Abacavir). An ABC dosing recommendation using PK simulation models has been endorsed by the World Health Organization (WHO) using weight-band dosing for full-term neonates. A recent study of infants with HIV in a South African cohort, stratified by age (<28 days and ≥28 days) and weight (<3 kg and ≥3 kg), demonstrated the safety and effectiveness of ABC in infants aged <3 months and in neonates weighing <3 kg.[8,16,17,46]

Table B. Advantages and Disadvantages of Anchor Drugs Recommended for Initial Antiretroviral Therapy Regimens in Infants From Birth to <30 Days of Age

Anchor Drugs[a]	Advantages	Disadvantages
DTG *(Preferred)*	• *Preferred* INSTI • Can be started at birth and continued through adulthood • Available as a single dose every other day for the first 2 weeks, followed by a daily dose thereafter • Available as a well-tolerated dispersible tablet suitable for use in neonates.	• Not yet FDA approved. ViiV/GSK to submit to FDA in January 2026. • Limited to use in term infants (≥37 weeks of gestation and weight ≥2 kg) or preterm infants with a postmenstrual age ≥37 weeks at the time of treatment initiation. • Every other day dosing during the first 2 weeks of life may be challenging for some caregivers. Additional education and/or dosing calendars, telephone reminders, or other adherence tools may be required.
RAL *(Alternative)*	• FDA-approved INSTI for use in term newborns weighing ≥2 kg • Produces rapid reduction in viral load • Safe and well tolerated • Avoids use of NVP and exposure to another class of ARVs (NNRTIs)	• First-generation INSTI with lower barrier to resistance than DTG or BIC • Granule formulation requires a multistep preparation before administration. • Caregivers must be taught how to properly prepare granule formulation. Explain that only a small volume of the prepared granule suspension is used; the rest must be discarded and cannot be reused. • Limited to use in term infants (≥37 weeks of gestation) or preterm infants with a postmenstrual age ≥37 weeks at the time of treatment initiation
NVP *(Alternative* for full-term infants and *Preferred* for preterm infants and term infants weighing <2 kg*)*	• Available in convenient oral solution • Can be used in preterm newborns with a gestational age ≥32 weeks • Extensive experience with NVP, including breastfeeding prophylaxis	• Not a *Preferred* ARV due to the potential for toxicity and development of viral resistance, although it can be used if clinically indicated • Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen • A single mutation can confer resistance to this drug and, in some instances, to all NNRTIs.

Table B. Advantages and Disadvantages of Anchor Drugs Recommended for Initial Antiretroviral Therapy Regimens in Infants From Birth to <30 Days of Age

Anchor Drugs[a]	Advantages	Disadvantages
LPV/r *(Alternative)*	• Available in convenient oral solution • More durable than RAL or NVP	• Should not be administered to neonates before a postmenstrual age of 42 weeks (calculated as gestational age at birth plus postnatal age) and a postnatal age <14 days • Poor palatability and bitter taste may cause incomplete dosing if infant spits it out. More side effects than other ARVs used in this age group.

[a] This table focuses on advantages and disadvantages regarding the selection of anchor drugs for ART regimens used in infants aged <30 days. Additional information is available in Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Infants and Children.

Key: ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; DTG = dolutegravir; FDA = U.S. Food and Drug Administration; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RAL = raltegravir

Practical and Clinical Considerations

The clinician should provide the infant's caregiver with information about prescribed medications, including names, doses, dose times, potential side effects, and how to properly administer the medications. Appropriately sized oral syringes should be dispensed, and liquid medications should include bottle adapter plugs to minimize wastage. Health care providers should counsel caregivers and provide opportunities to practice preparing and administering the prescribed medications, and document such interactions in the medical record; such practice is especially important when DTG or RAL is prescribed. For DTG, every other day dosing during the first 2 weeks of life may be challenging for some caregivers. Adherence aids, such as dosing calendars, telephone reminders, and/or mobile reminders, are recommended when appropriate. For RAL, there is added complexity due to the multistep process to prepare the infant dose using the oral granules for suspension and changes in dosing during the first few weeks of life (see Raltegravir).

ARV availability and complexity of preparation and administration may affect decisions about the use of NVP versus DTG. It is recommended that a medication calendar be provided and that the caregiver be involved in deciding the most convenient times for the medications to be administered. Some caregivers may prefer a more discreet medication reminder (e.g., pocketsize folding calendar) or no reminders at all. It is important that the infant's caregiver is actively involved in these discussions. Clinicians should ensure that insurance covers the prescribed ART regimen and that the infant's local pharmacy stocks all components of the regimen. For neonates who are initiating ART while still in the hospital, clinicians should provide caregivers with the appropriate information and an initial supply of medications before discharge.

At each clinic visit, the clinician and caregiver should review the process of preparing the different liquid formulations of the medications to ensure that correct volumes and doses are being administered. When appropriate, weight-band dosing should be used and doses should be adjusted based on weight gain and age. This adjustment is particularly important during the first weeks of life, when changes to drug metabolism and renal function occur that impact appropriate dosing recommendations (see Appendix A. Pediatric Antiretroviral Drug Information). Refills should be arranged with pharmacies that stock the ARV drugs.

Special Situations

- **ARV Drug Resistance:** Infants can acquire HIV infection with drug-resistant virus. Transmitted drug resistance has been demonstrated with NNRTIs, NRTIs, PIs, and INSTIs, although transmitted resistance to INSTIs is very rare.[47] Therefore, when viral suppression has not been achieved during pregnancy and drug resistance is suspected, the parent's ARV resistance data should be reviewed, if available, and consultation with a pediatric HIV expert is recommended. In neonates, a *Preferred* ART regimen should be commenced immediately; this regimen may later be changed or modified based on the results of baseline infant HIV genotyping (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).
- **HIV-2 Infection:** ART regimens for infants with HIV-2 infection only or infants with HIV-2 and HIV-1 coinfection should include ARVs that are active against HIV-2. Because NNRTIs are not active against HIV-2, NVP should not be used. A RAL-based regimen is recommended for infants with HIV-2 or with HIV-2 and HIV-1 coinfection: RAL (for full-term infants weighing ≥2 kg) plus ZDV plus (3TC or FTC). Consultation with a pediatric HIV expert or the National Perinatal HIV/AIDS Hotline (1-888-448-8765) is recommended for the care of infants weighing <2 kg or with a gestational age <37 weeks.

Planning Antiretroviral Transitions

Although the ARV regimen started in the first 29 days of life can be continued, the Panel recommends that consideration be given to changing the regimen to a DTG-containing regimen after the infant reaches the appropriate age and weight if the infant did not initially receive a DTG-containing regimen; see *Preferred* Regimens in Recommended Initial ART Regimens for Infants and Children Aged ≥30 Days to <2 Years below. This change should be considered because DTG has greater efficacy and durability than NVP,[48] DTG dispersible tablets are easier to prepare and administer than RAL granules, and DTG is available in an FDC formulation (DTG/FTC/ABC). A negative test for the HLA-B*5701 allele must be obtained before initiating a regimen of DTG plus ABC plus 3TC (see Recommended Initial ART Regimens for Infants and Children Aged ≥30 Days to <2 Years below).

Recommended Initial Antiretroviral Therapy Regimens for Infants and Children Aged ≥30 Days to <2 Years

Preferred Regimens

- Aged ≥30 days to <2 years: ART should be initiated with a DTG-based regimen. Transition to a DTG-based regimen should be considered if an infant is initiated on an NVP-, RAL-, or LPV/r-based regimen in the first month of life.
  - DTG plus ABC plus (3TC or FTC) if HLA-B*5701 negative ***or***
  - DTG plus ZDV plus (3TC or FTC) ***or***
- Aged ≥3 months to <2 years and weighing ≥6 kg to <25 kg
  - DTG plus ABC plus 3TC as an FDC (Triumeq PD) if HLA-B*5701 negative

For preterm infants who have not yet achieved a postmenstrual age of 37 weeks at 30 days of age, therapy should be initiated using the recommended initial ART regimen for preterm infants, with NVP

as the anchor drug (see Initial ART Regimens for Infants From Birth to <30 Days of Age above) and transitioning to a DTG-based regimen when postmenstrual age is ≥37 weeks and weight is ≥2 kg.

The Panel supports the use of the single ABC/3TC/DTG FDC dispersible tablet as an alternative to the separate formulations of ABC, 3TC, and DTG in infants weighing ≥3 kg to <6 kg and aged ≥4 weeks to facilitate treatment adherence. Although this FDC is not FDA-approved in this population, the Panel's recommendation is based on population PK modeling of data from IMPAACT 2019, IMPAACT P1093, ODYSSEY clinical trials for DTG, and the PETITE clinical trial for ABC and 3TC.[2,17,18,49-51]

Rationale

It is assumed that all children in this age group are unable to swallow pills and will require treatment with ARVs in liquid, dispersible tablet, powder packet, or chewable tablet formulations.

For infants and children who are starting ART at ≥30 days of age, the Panel recommends initiating an INSTI-based ART regimen using DTG plus two NRTIs. DTG is a second-generation INSTI that has a higher barrier to resistance than RAL and is FDA approved for use in this age group. While there is low potential for development of resistance with DTG, young infants may initially have very high HIV viral loads and continue to have low-level viremia during the first year of life. The overall risk of developing resistance with DTG-based ART in young infants is unknown.

INSTIs have better efficacy and safety profiles than NNRTIs or PIs, and DTG has been studied extensively in children.[2,4,52] Importantly, the FDC of DTG/ABC/3TC has proven efficacy and a good safety profile, with weight-band dosing that achieves PK targets[49,52,53].

For infants aged ≥30 days to ≤6 weeks still receiving presumptive HIV therapy with RAL or NVP plus two NRTIs at the time of HIV diagnosis, the Panel recommends changing to one of the DTG-based regimens listed above using DTG dispersible tablets. The liquid formulations of the NRTIs used as part of presumptive HIV therapy (usually ZDV plus 3TC) can be continued; no change in NRTIs is required.

Alternative Regimens

Alternative Anchor Drugs

- **LPV/r:** LPV is available as an oral solution coformulated with RTV, and twice-daily dosing is recommended. LPV/r should be administered with food to improve tolerability.[39,54,55] Poor taste and palatability of the oral solution may become an issue for young children and limit acceptance of this regimen. LPV/r has a high genetic barrier to drug resistance. However, poor acceptance of formulation, gastrointestinal side effects, and poor weight gain may limit its use in this age group.[56]
- **ATV/r:** ATV/r can be considered an *Alternative* to LPV/r in children weighing ≥15 kg.[57] ATV and RTV are available as separate powder packets that are mixed with either soft food or formula and administered once daily. The powder formulation of ATV can be used in children weighing ≥15 kg to <25 kg. The powder formulations have poor palatability and may be difficult to tolerate in this age group.
- **NNRTIs:** NVP could be considered if there is resistance or intolerance to both PIs and INSTIs. However, NVP is generally not recommended as an initial treatment in this age group because the low genetic barrier to resistance during a time of significant viremia may lead to drug resistance to all members of the NNRTI class of drugs.[40] Efavirenz (EFV) is not recommended

for children <3 years of age due to highly variable PK in young children, difficulty in determining an appropriate dose without therapeutic drug monitoring, and side effects (i.e., neurologic toxicity).[58]

Nucleoside Reverse Transcriptase Inhibitor Backbones in *Alternative* Regimens

- Twice-daily dosing: An NRTI backbone of ZDV plus 3TC twice daily or ABC plus 3TC twice daily allows for all medications to be administered at the same time when given in combination with LPV/r or RAL. There is considerable experience with ZDV and 3TC in this age group. ABC is associated with less bone marrow toxicity than ZDV and may be the *Preferred* NRTI for long-term use.

Practical and Clinical Considerations

DTG plus ZDV plus 3TC can be initiated immediately. However, due to the potential of ABC hypersensitivity, a negative test for the HLA-B*5701 allele must be obtained before initiating a regimen of DTG plus ABC plus 3TC. HLA-B*5701 should be included in the initial work-up for all infants and children with HIV. ABC is not FDA approved for use in infants aged <3 months, but the Panel does recommend use of twice-daily ABC for infants aged ≥30 days. In decisions about selecting ABC as a component of the initial regimen for children aged <2 years, clinicians should consider concerns regarding delays initiating treatment related to HLA-B*5701 testing versus the advantages of using an FDC.

DTG is available as dispersible tablets that are administered separately, along with the liquid formulations of ZDV and 3TC. For infants and children weighing ≥6 kg to <25 kg who are initiating therapy at ≥3 months of age, DTG plus ABC plus 3TC is available as dispersible FDC tablets (Triumeq PD) that can be administered once daily and that provide a number of advantages:

- Tablets are mixed in water (volume depends on the number of tablets needed for weight-band dosing; see Dolutegravir for details about dosing and preparation).
- Once-daily dosing improves adherence to ARVs.
- Use of the FDC formulation avoids the need to measure and administer liquid ZDV and 3TC separately and minimizes difficulties in accurately measuring the volumes needed.
- Use of the FDC minimizes the need to adjust doses frequently as the infant or child grows.

When teaching families about preparing the medications, it should be explained that dispersible tablets need to be mixed in water because of the lack of data about dispersing DTG or DTG/ABC/3TC dispersible tablets in other liquids, such as formula or breast milk. With once-daily dosing, it is particularly important to emphasize the critical importance of adhering to all scheduled doses.

Special Situations

- **DTG dispersible tablets not available:** If DTG dispersible tablets are not available, RAL can be administered using either the oral granules for suspension dispersed in water or the chewable tablets dispersed in juice or formula/milk.[59] RAL oral granules for suspension require a multistep process to prepare each dose, and twice-daily dosing is required. RAL also has a lower genetic barrier to resistance than DTG.

- **Identification of viral resistance:** If viral resistance is identified in baseline genotype testing, the initial ART regimen may need to be modified.
    - **INSTI resistance:** If resistance to INSTIs is present, the regimen should consist of the NRTI backbone plus a boosted PI. Use of LPV/r is recommended in this situation because it is coformulated with ritonavir in a formulation suitable for administration in this age group. In case of multidrug ARV resistance, consultation with a pediatric HIV expert is recommended.
    - **M184V resistance mutation:** If the M184V/I mutation associated with FTC and 3TC is present, these medications should be continued if the new regimen contains TDF, TAF, or ZDV. The presence of this mutation may increase susceptibility to these NRTIs.
- **HLA-B*5701 positive:** If a child tests positive for HLA-B*5107, ART regimens with ABC should not be given because of ABC-associated hypersensitivity.
- **HBV infection:** In HIV/HBV coinfection, an ART regimen should include two NRTIs active against HBV (see Selection of Dual–Nucleoside Reverse Transcriptase Inhibitor Backbone as Part of Initial Antiretroviral Therapy Regimens above). However, regimens containing only one active NRTI (3TC or FTC) may be used when children in this age group do not meet the weight criteria for use of a second NRTI active against HBV. Children in this age group should be switched to a TAF/FTC-containing regimen as soon as possible after they weigh ≥14 kg.
- **HIV-2 infection:** ART regimens for infants and children with HIV-2 infection only or those with HIV-2/HIV-1 coinfection should include ARVs that are active against HIV-2. Consultation with a pediatric HIV expert is recommended for the care of infants and children with HIV-2.

Planning Antiretroviral Transitions

For infants aged ≥3 months and weighing ≥6 kg who previously initiated treatment on DTG plus ZDV plus (3TC or FTC), the Panel recommends changing to a regimen of once-daily DTG plus ABC plus 3TC that is available as dispersible FDC tablets (Triumeq PD) in order to simplify measurement of ARV doses and administration. A negative test for the HLA-B*5701 allele must be obtained prior to initiating an ABC-containing regimen.

Additional options are available for transitioning to other INSTI-containing preparations as children become older and are able to swallow pills, such as the FDC BIC/FTC/TAF (Biktarvy), which can be used in children aged ≥2 years and weighing ≥14 kg (see discussion in Recommended Initial ART Regimens for Children Aged ≥2 Years to <12 Years below). The NRTI backbone FTC/TAF is available in an FDC (Descovy) that can be used in combination with an anchor drug, such as DTG, in children weighing ≥14 kg who are able to swallow pills.

Recommended Initial Antiretroviral Therapy Regimens for Children Aged ≥2 Years to <12 Years

Preferred Regimens

When planning an initial ART regimen for children aged ≥2 years to <12 years, consider that some children, particularly younger children, may not be able to swallow pills, whereas older children may be able to take pills. It is recommended that clinicians counsel families about teaching children how to swallow pills because that ability increases the number of ARV options and simplifies regimens.[60] Children as young as 4 years of age can be taught how to swallow pills. In addition to age and ability to swallow pills, the weight of the child must also be taken into consideration. Therefore, the Panel recommendations for what regimen to start are presented for children unable to swallow pills and those who are able. FDA-approved pill formulations are based on a child's weight, followed by

recommendations for those who are able to swallow pills and the minimum weight allowed for dosing. Please refer to Appendix A. Pediatric Antiretroviral Drug Information for specific dosing of ARV drugs by weight band.

Preferred Regimens for Children Aged ≥2 Years to <12 Years Who Are Not Able to Swallow Pills

- DTG plus ABC plus 3TC in the dispersible FDC formulation (Triumeq PD) for children weighing 6 kg to <25 kg if HLA-B*5701 negative ***or***
    - DTG film-coated tablets (Tivicay) plus ABC plus (3TC or FTC) in liquid formulations for children weighing ≥25 kg if HLA-B*5701 negative (see Dolutegravir for special instructions about administering DTG tablets to children who are not able to swallow pills)
- DTG plus FTC plus TAF for children weighing ≥14 kg (see Dolutegravir and Tenofovir Alafenamide for available formulations of DTG [Tivicay, Tivicay PD], dosage strengths of FTC/TAF [Descovy], and special instructions for administering DTG film-coated tablets and FTC/TAF tablets to children who are not able to swallow pills) ***or***
- DTG in dispersible tablets plus ZDV plus (3TC or FTC) in liquid formulations

The dispersible FDC tablet of DTG/ABC/3TC (Triumeq PD) is a once-daily regimen shown to be efficacious in the Phase 1/2 IMPAACT 2019 study among children aged <12 years and weighing 6 kg to 40 kg.[53] A child must have a negative HLA-B*5701 allele screening test before initiating treatment to ensure that the child will not be at risk for a hypersensitivity reaction to ABC.

When the DTG/ABC/3TC dispersible FDC tablet cannot be used (i.e., it is not available or results of HLA-B*5701 testing are unknown or positive) and the child weighs <14 kg at treatment initiation, the Panel recommends initiating a regimen of DTG plus ZDV plus 3TC. DTG is available as dispersible tablets (Tivicay PD) dosed once daily, which can be used in children weighing 6 kg to <25 kg. ZDV and 3TC are both available in liquid formulations and require twice-daily dosing. If DTG/ABC/3TC cannot be used and the child weighs ≥14 kg, DTG plus FTC/TAF (Descovy) is recommended by the Panel. FTC/TAF (Descovy) is available in two different-strength tablets, with the lower-strength tablet for children weighing ≥14 kg to <25 kg.

Preferred Regimens for Children Aged ≥2 Years to <12 Years Who Are Able to Swallow Pills

For children weighing <14 kg, see regimens listed above for children who are not able to swallow pills.

- BIC plus FTC plus TAF (FDC BIC/FTC/TAF, Biktarvy) for children weighing ≥14 kg
- DTG plus FTC plus TAF (DTG, Tivicay, plus the FDC FTC/TAF, Descovy) for children weighing ≥14 kg
- DTG plus ABC plus 3TC (FDC DTG/ABC/3TC, Triumeq) for children weighing ≥25 kg if HLA-B*5701 negative

Rationale

The Panel recommends initiating ART with a once-daily, single-tablet regimen of BIC/FTC/TAF (Biktarvy) for children weighing ≥14 kg. Two different strengths of BIC/FTC/TAF tablets are available, with the lower-strength tablet for children weighing ≥14 kg and <25 kg. The product label states that for children who are unable to swallow a whole tablet, the BIC/FTC/TAF tablet can be split and each

part taken separately, as long as all parts are ingested within approximately 10 minutes.[61]

DTG/3TC/ABC (Triumeq) is another *Preferred* single-tablet regimen option for children weighing ≥25 kg.[52]; however, the DTG/3TC/ABC pill is much larger than the BIC/FTC/TAF pill and might be more challenging to swallow, particularly for younger children. If DTG/3TC/ABC is selected, documentation of a negative HLA-B*5701 screening should occur prior to treatment initiation. For children weighing ≥14 kg, the film-coated tablet of DTG (Tivicay) used in conjunction with the FDC tablets of FTC/TAF (Descovy) is also recommended by the Panel.

The FDC of BIC/FTC/TAF (Biktarvy) has been studied in adolescents aged 12 years to <18 years and weighing ≥35 kg (Cohort 1), children aged 6 years to <12 years and weighing ≥25 kg (Cohort 2), and children aged ≥2 years and weighing ≥14 kg to <25 kg (Cohort 3). 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.[62] Among children in Cohort 3, after 24 weeks, all 12 participants maintained viral suppression.

DTG, studied in the multinational open-label IMPAACT 1093 study[2,63,64] and ODYSSEY,[3,15,65] has been demonstrated to be safe, efficacious, and well tolerated in children. The dispersible tablet formulation of the FDC ABC 60 mg/DTG 5 mg/3TC 30 mg (Triumeq PD) was studied in IMPAACT P2019 to confirm dosing of the three-drug FDC in children aged <12 years. In IMPAACT P2019, children were dosed in five weight bands aligned with WHO-preferred weight bands. Results of the initial PK and safety assessments for 35 participants in weight bands ≥6 kg demonstrated acceptable PK parameters and tolerability for all cohorts and confirmed dosing according to WHO weight bands.[49]

Alternative Regimens

Anchor Drugs

When concern for INSTI resistance exists, the following anchor drugs represent *Alternative* treatment options when paired with two fully active NRTIs.

- **ATV plus RTV or COBI:** ATV is available as a powder packet that should be mixed with solid food and administered once daily. ATV powder can be coadministered with RTV once daily for a child ≥3 months and weighing ≥5 kg to ≤25 kg. However, because RTV oral solution is no longer commercially available, use of ATV/r is limited to children weighing ≥15 kg who can use the RTV 100-mg powder packet or 100-mg tablet. The RTV powder formulation has poor palatability and may be difficult to tolerate. For a child weighing ≥15 kg who can swallow pills, the capsule formulation of ATV can be dosed once daily with the RTV tablets (i.e., ATV/r) in children who are ≥6 years of age. Boosting ATV with COBI is an option only if the child weighs ≥35 kg and can swallow pills and is available as a FDC of COBI-boosted ATV (ATV/c) that can be administered once daily.
- **DRV plus RTV or COBI:** DRV is an option for children aged ≥3 years to <12 years and weighing ≥20 kg. However, DRV requires a PK enhancer or boosting agent, such as RTV or COBI. DRV is available as a solution or tablet that can be administered twice daily with an RTV powder packet or tablet. Boosting DRV with COBI is an option only if the child weighs ≥25 kg. COBI-boosted DRV (DRV/c) is available in a once-daily FDC (Prezcobix), with two strengths available, DRV/c

675 mg/150 mg for children weighing ≥25 kg to <40 kg and DRV/c 800 mg/150 mg for those weighing ≥40 kg.

- **NNRTIs:** An NNRTI-based regimen using NVP, EFV, or doravirine (DOR) could be considered in the case of resistance or intolerance to both PIs and INSTIs. EFV is not recommended by the Panel for use in children aged <3 years due to highly variable PK in young children, difficulty in determining an appropriate dose without therapeutic drug monitoring, and side effects (i.e., neurologic toxicity) (see Efavirenz). DOR is approved for use in children weighing ≥35 kg, and recent data found that once-daily dosing of DOR/3TC/TDF was safe and well tolerated for maintaining viral suppression through 96 weeks in adolescents.[66]

Practical and Clinical Considerations

The availability of FDC formulations and method of administration are important considerations in the selection of a *Preferred* initial regimen.

- BIC/FTC/TAF (Biktarvy) is a single-tablet regimen for children weighing ≥14 kg. The tablet may not be crushed or dissolved; however, it can be split in half prior to dosing for ease of swallowing. BIC/FTC/TAF is available in two formulations for children able to swallow pills, including BIC 30 mg/FTC 120 mg/TAF 15 mg for children weighing ≥14 kg to <25 kg and BIC 50 mg/FTC 200 mg/TAF 25 mg for children weighing ≥25 kg.
- ABC/DTG/3TC (Triumeq PD) is a dispersible tablet that can be used in children weighing <25 kg and should be dissolved in water. Each tablet contains all three drugs. The number of tablets per dose is based on a child's weight.
- ABC/DTG/3TC (Triumeq) is a nondispersible, single-tablet regimen option for children weighing ≥25 kg who are able to swallow whole pills. However, a disadvantage is the larger pill size, which can make swallowing challenging compared with the other recommended options.
- DTG plus FTC/TAF is dosed once daily. DTG is available as dispersible tablets (Tivicay PD) and as a film-coated tablet (Tivicay). FTC/TAF (Descovy) is available in two different strengths as a single tablet to be swallowed. See Dolutegravir and Tenofovir Alafenamide for specific weight parameters and for special instructions about administering these ARVs to children who are not able to swallow pills.

Special Situations

- Identification of viral resistance: If viral resistance is identified in baseline genotypic testing, the initial ART regimen may need to be modified.
  - **INSTI resistance:** If resistance to INSTIs is present, the regimen should consist of the NRTI backbone plus a boosted PI. PI options include ATV or DRV, both of which should be boosted with either RTV or COBI. See *Alternative* Regimens Anchor Drugs above for age and weight restrictions for each PI in conjunction with its formulation and its boosting agent. In the case of multidrug ARV resistance, consultation with a pediatric HIV expert is recommended.
  - **M184V resistance mutation:** Regimens should contain at least two, but preferably three, fully active drugs for durable and potent virologic suppression. If the M184V/I mutation associated with FTC and 3TC is present, these medications should be continued if the regimen contains TDF, TAF, or ZDV. The presence of this mutation may increase susceptibility to these NRTIs.
- **HLA-B*5701 positive:** If a child tests positive for HLA-B*5107, ARV regimens with ABC should be avoided because of ABC-associated hypersensitivity.

- **HBV infection:** The ART regimen should include two NRTIs active against HBV (see Selection of Dual–Nucleoside Reverse Transcriptase Inhibitor Backbone as Part of Initial Antiretroviral Therapy Regimens above). The Panel recommends the FDC FTC/TAF (Descovy) as the NRTI backbone for children with HIV/HBV coinfection.
- **HIV-2 infection:** ART regimens for children with HIV-2 infection only or those with HIV-2/HIV-1 coinfection should include ARVs that are active against HIV-2. Consultation with a pediatric HIV expert is recommended for the care of infants and children with HIV-2.

Planning Antiretroviral Transitions

For children aged ≥2 years to <12 years who initiated treatment when they were unable to swallow pills or whose weight precluded use of a pill option, when they can swallow pills and are of an appropriate age and weight, the Panel recommends transitioning to the once-daily FDC of BIC/FTC/TAF (Biktarvy), so long as there are no contraindications.

Recommended Regimens for Children and Adolescents Aged ≥12 Years

Recommendations for initial ART regimens for adolescents are addressed in What to Start in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV (also see Adolescents and Young Adults With HIV); an overview is provided here.

Pubertal changes during adolescence encompass increased growth velocity, changes in body composition, and development of secondary sexual characteristics. It is recognized that these changes can affect the PK and pharmacodynamics of drugs. Adolescents with perinatal HIV infection are more likely to have delayed puberty and growth compared with their uninfected peers.[67] However, regimens recommended for initial ART in the Adult and Adolescent Guidelines provide adequate drug exposure and are effective and safe when used for people with HIV in this age bracket above a minimum weight, regardless of pubertal stage.

Preferred Regimens

Preferred regimens for adolescents aged ≥12 years starting treatment should have the following characteristics: (a) preferably be available as a once-daily FDC single-tablet regimen for ease of use, (b) have a high barrier to resistance, (c) be well tolerated, and (d) have demonstrated clinical efficacy and safety with long-term use. For adolescents who do not have a prior history of using long-acting cabotegravir (CAB-LA) for HIV preexposure prophylaxis (PrEP), *Preferred* ART regimens are listed below.

- BIC plus FTC plus TAF (FDC BIC/FTC/TAF, Biktarvy) for adolescents weighing ≥25 kg
- DTG plus FTC plus TAF (FDC FTC/TAF, Descovy) for adolescents weighing ≥35 kg

DRV-based regimens are recommended for initial therapy in adolescents who previously received CAB-LA for PrEP (see *Alternative* Regimens below).

In the unlikely event that an adolescent aged ≥12 years is not able to swallow pills or weighs <25 kg, please refer to the *Preferred* Regimens for children ≥2 years to <12 years above and Table 8 below.

Rationale

The *Preferred* regimens (BIC/FTC/TAF and DTG/FTC/TAF) are consistent with the Panel's recommendations for children ≥2 years to <12 years and contain the appropriate dose of the three drugs for the specified weight. These regimens are also the same as those recommended for use in adults and adolescents without delay in pubertal onset, allowing for the continuation of the same initial *Preferred* regimen as people transition through puberty from adolescence to adulthood. Whereas BIC/FTC/TAF is an FDC, DTG/FTC/TAF is a two-drug regimen of DTG along with the FDC of FTC/TAF.

Alternative Regimens

- DTG plus 3TC (FDC DTG/3TC, Dovato) for adolescents weighing ≥25 kg
- DTG plus ABC plus 3TC (FDC DTG/ABC/3TC, Triumeq) for adolescents weighing ≥25 kg
- DRV/c plus TAF plus FTC (FDC DRV/c/TAF/FTC, Symtuza) for adolescents weighing ≥40 kg
- DRV/c (FDC, Prezcobix) plus TDF/FTC (FDC, Truvada) for adolescents weighing ≥40 kg

The FDC of DTG/3TC was shown to be efficacious in adolescents naive to treatment aged ≥12 years to ≤18 years at 96 weeks of treatment in the DANCE study[68] and represents an alternative to BIC/FTC/TAF in adolescents ≥12 years of age and weighing ≥25 kg in whom ABC, TAF, or TDF cannot be used or are not optimal. DTG/3TC can be used as an initial regimen for adolescents with HIV who have a plasma HIV-1 RNA ≤500,000 copies/mL with genotypic resistance testing available that demonstrates sensitivity to 3TC; have no prior exposure to CAB-LA PrEP; or, in the case of prior exposure to CAB-LA, have documented INSTI sensitivity on genotypic resistance testing. If HIV/HBV coinfection is present, another HBV-active drug should be added. Although the second option (DTG/ABC/3TC) is available as a convenient FDC regimen, HLA-B*5701 testing must be performed before initiating therapy. Due to the risk of ABC-related cardiovascular events and the availability of alternative options for initial therapy in this age group, this regimen is no longer recommended as *Preferred*. Boosted DRV regimens are approved for use in adolescents and can be used if concerns exist about INSTI resistance (e.g., adolescents diagnosed with HIV who have a history of CAB-LA use for PrEP). Boosted DRV regimens give the provider a choice between using a TAF-containing regimen as a single daily FDC tablet or a TDF-containing regimen consisting of two daily tablets. Choices for the boosted DRV regimens should be driven by concern for renal and bone disease (i.e., the need to avoid TDF) or adverse weight or lipid issues (i.e., the need to avoid TAF).

Practical and Clinical Considerations

Clinicians should provide the education and support that caregivers and adolescents need to be able to administer or take ARVs correctly and adhere to the ART regimen (see Adherence to Antiretroviral Therapy in Children and Adolescents With HIV). Adolescents may have difficulty adhering to daily oral medications. Among many other factors, the number of pills and the pill size are important considerations. Additionally, when considering the optimal regimen for initiation, the clinician should understand whether the adolescent will be supervised to take treatment or will be expected to take their treatment independently. *Preferred* initial therapy with a single tablet dosed once daily helps maintain adherence and viral suppression. Biktarvy is one of the smallest FDC single-tablet regimens currently available (see Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents).

Several other issues unique to adolescents need to be addressed when initiating HIV treatment. Some may be living with caregivers who are not aware of their diagnosis and may still be accessing

care under their parent or caregiver's health insurance plan. Communications between health insurance companies and caregivers can compromise confidentiality and result in accidental disclosure. Clinicians and social workers need to work around this issue, and in some instances, assist the individual in establishing their own access to HIV drugs and/or health insurance. Some adolescents may be emancipated and living on their own but need access to affordable health insurance. In other instances, adolescents with HIV have been rejected by their families and are homeless. Rapid initiation of HIV treatment, although desirable, may have to be deferred until social barriers to adherence are addressed. Adolescents may have other comorbidities, such as depression and increased risk for suicide. These are heightened in adolescents whose sexual/romantic attractions and/or self-expression are less common. Food insecurity and other social determinants of health that can affect an adolescent's ability to safely initiate and adhere to HIV treatment should be evaluated and available support offered, if possible. Finally, use of patient-centered language can be beneficial in establishing and maintaining rapport with adolescents, facilitating sustained engagement in care. For additional information, see Special Considerations for Antiretroviral Therapy Use in Adolescents With HIV and Adolescents and Young Adults With HIV in the Adult and Adolescent Antiretroviral Guidelines.

Special Situations

If weight gain and increased risk for clinical obesity is a concern, or if the adolescent has a high-risk lipid profile, a TAF-containing regimen may not be an appropriate component of a preferred initial regimen (see Selection of Dual–Nucleoside Reverse Transcriptase Inhibitor Backbone as Part of Initial Antiretroviral Therapy Regimens, above). An FDC single-tablet regimen containing the NNRTI DOR with a backbone of TDF/FTC can be considered when initiating treatment in adolescents with these concerns.[66] However, providers must take into account the risks of proximal tubular injury, rare irreversible renal failure, and decreased BMD that can occur when TDF is used.

Planning Antiretroviral Transitions

Adherence to daily oral medications is particularly challenging for adolescents,[69,70] resulting in low rates of virologic suppression compared to adults.[71] CAB and RPV (Cabenuva) is a two-drug long-acting (LA) ART regimen administered as two intramuscular injections given every two months that is approved for adolescents weighing ≥35 kg and adults with HIV who are virologically suppressed on an oral regimen. Although long-acting cabotegravir plus rilpivirine (LA CAB/RPV) is not an option for initial therapy, it provides an option for adolescents who wish to maintain viral suppression without the need for daily oral medications. In select circumstances, some adolescents experiencing difficulties with adherence to an oral ART regimen could receive intensive adherence support to achieve viral suppression on their initial regimen as a bridge to switching to LA CAB/RPV (see Management of Children Receiving Antiretroviral Therapy: Modifying Antiretroviral Regimens in Children With Sustained Virologic Suppression on Antiretroviral Therapy).[72]

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

The Panel designates regimens as *Preferred* based on efficacy, ease of administration, acceptable toxicity, and other considerations. *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 by weighing the advantages and disadvantages of each combination (see Table A. Factors to Consider When Selecting an Antiretroviral Treatment Regimen for Infants, Children and Adolescents, above, and Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Infants and Children, below).

Many agents have multiple formulations, as well as age and weight recommendations. Refer to Appendix A. Pediatric Antiretroviral Drug Information for additional information and recommended doses and formulations. 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 Infants With In Utero, Intrapartum, or Breastfeeding Exposure to HIV.

Children who are receiving effective and tolerable antiretroviral 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 additional guidance about transitioning children to other regimens as they grow.

Panel recommendations for children and adolescents aged ≥12 years are not included in this table; see Recommended Regimens for Children and Adolescents Aged ≥12 Years in the text.

See the Adult and Adolescent Antiretroviral Guidelines for recommendations about initial antiretroviral therapy for adolescents.

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

***Preferred* Initial Regimens and ARV Drugs Based on Age and Weight at Time of Treatment Initiation** **8A. Infants From Birth to <30 Days of Age**			
Panel Recommendation[a,b]	**Regimen or ARV Drug**	**Age and/or Weight Restriction[c]**	**Formulations and Comments[c]**
Preferred ART regimens **for infants ≥37 weeks of gestation and aged <30 days and preterm infants with a postmenstrual age of ≥37 weeks at treatment initiation**	**INSTI (DTG) plus two NRTIs** • DTG plus ZDV plus (3TC or FTC) • NVP plus ZDV plus (3TC or FTC)	≥2 kg (DTG) <2 kg at birth (NVP)	Dispersible tablet for oral suspension (DTG) plus oral solutions for NVP, ZDV plus (3TC or FTC)
Preferred ART regimen **for preterm infants ≥32 to <37 weeks of gestation**	**NNRTI (NVP) plus two NRTIs** • NVP plus ZDV plus (3TC or FTC)	None	All oral solutions
Preferred ART regimens **for preterm infants <32 weeks of gestation**	Consultation with a pediatric HIV expert or the National Perinatal HIV/AIDS Hotline (1-888-448-8765) is recommended		
Alternative ART regimens **for infants**	**PI (LPV/r) plus two NRTIs** • LPV/r plus ZDV plus (3TC or FTC)	Postmenstrual age ≥42 weeks and a postnatal age of >14 days (LPV/r)	All oral solutions
	NNRTI (NVP) plus two NRTIs • NVP plus ZDV plus (3TC or FTC)	≥32 weeks of gestation	All oral solutions
	INSTI (RAL) plus two NRTIs • RAL plus ZDV plus (3TC or FTC)	≥2 kg (RAL)	RAL granules for oral suspension plus oral solutions for ZDV plus (3TC or FTC)
Alternative NRTI backbone **for infants**	• ABC plus (3TC or FTC) if HLA-B*5701 negative	≥37 weeks of gestation	All oral solutions Use of ABC[d] requires negative HLA-B*5701 results.

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

***Preferred* Initial Regimens and ARV Drugs Based on Age and Weight at Time of Treatment Initiation** **8B. Infants and Children Aged ≥30 Days to <2 Years**			
Panel Recommendation[a,b]	**Regimen or ARV Drug**	**Age and/or Weight Restriction[c]**	**Formulations and Comments[c]**
Preferred ART regimens **for infants and children aged ≥30 days to <2 years**	**INSTI (DTG)[e,f] plus two NRTIs** • DTG plus ZDV plus (3TC or FTC) *or*	DTG ≥30 days and ≥3 kg to <25 kg	DTG dispersible tablets plus oral solutions (ABC[d], ZDV, 3TC, or FTC)
	• DTG plus ABC plus (3TC or FTC) if HLA-B*5701 negative	DTG ≥30 days and ≥3 kg to <25 kg	
	• DTG/ABC/3TC in FDC if HLA-B*5701 negative	≥3 months and ≥6 kg to <25 kg (Triumeq PD)	DTG/ABC/3TC in FDC dispersible tablets (Triumeq PD)
		≥25 kg (Triumeq)	DTG/ABC/3TC FDC tablets if ≥25 kg (Triumeq). See Dolutegravir for special instructions if a child is unable to swallow pills.
Alternative anchor drugs to replace DTG in an ART regimen with a *Preferred* NRTI backbone **for infants and children aged ≥30 days to <2 years**	**Boosted PI** • LPV/r[f] (boosted PI)	Postmenstrual age ≥42 weeks and postnatal age >14 days	LPV/r is available in an oral solution.
	• ATV plus RTV (boosted PI)	ATV ≥15 kg to <25 kg	ATV is available in powder packets; RTV is available in 100-mg tablets and 100-mg powder packets.
	NNRTI NVP (NNRTI)	<3 years	NVP is available in an oral solution.

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

***Preferred* Initial Regimens and ARV Drugs Based on Age and Weight at Time of Treatment Initiation** **8C. Children Aged ≥2 Years to <12 Years**			
Panel Recommendation[a,b]	**Regimen or ARV Drug**	**Age and/or Weight Restriction[c]**	**Formulations and Comments[c]**
Preferred ART regimens **for children aged ≥2 years to <12 years who are unable to swallow pills**	**INSTI (DTG) plus Two NRTIs**		**For children who are unable to swallow pills**
	• DTG/ABC/3TC in FDC if HLA-B*5701 negative	≥3 months and 3 kg to <25 kg (Triumeq PD)	DTG/ABC/3TC is available in FDC dispersible tablets (Triumeq PD).
	• DTG plus ZDV plus (3TC or FTC)	≥30 days and ≥3 kg (DTG)	DTG is available in dispersible tablets and taken with oral solutions (ZDV, 3TC, or FTC).
	• DTG plus FTC/TAF; FTC/TAF in FDC (Descovy)	≥30 days and ≥3 kg (DTG) ≥14 kg to <25 kg (FTC/TAF)	TAF is available as FTC/TAF in FDC (Descovy) only, not as an individual drug. See Tenofovir Alafenamide for special instructions about administering FTC/TAF to children who are not able to swallow pills. For children who are ≥25 kg and unable to swallow pills, see Dolutegravir and Tenofovir Alafenamide for special instructions about administering DTG 50 mg and FTC/TAF (FTC 200 mg/TAF 25 mg).

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

***Preferred* Initial Regimens and ARV Drugs Based on Age and Weight at Time of Treatment Initiation** **8C. Children Aged ≥2 Years to <12 Years**			
Panel Recommendation[a,b]	**Regimen or ARV Drug**	**Age and/or Weight Restriction[c]**	**Formulations and Comments[c]**
Preferred ART regimens **for children aged ≥2 years to <12 years who are able to swallow pills**	**INSTI (BIC or DTG) plus Two NRTIs**		**For children who are able to swallow pills**
	• BIC plus FTC plus TAF in FDC[g,h]	Aged ≥2 years and ≥14 kg to <25 kg (BIC 30 mg/FTC 120 mg/ TAF 15 mg) ≥25 kg (BIC 50 mg/FTC 200 mg/TAF 25 mg)	BIC is available only in the FDC BIC/FTC/TAF. The product label states that for children who are unable to swallow a whole tablet, the BIC/FTC/TAF tablet can be split and each part taken separately, as long as all parts are ingested within approximately 10 minutes; see Bictegravir.
	• DTG plus ABC plus 3TC in FDC if HLA-B*5701 negative	≥25 kg	DTG/ABC/3TC is available in FDC tablets (Triumeq).
	• DTG plus FTC/TAF; FTC/TAF in FDC (Descovy)[i]	≥14 kg (DTG tablets [Tivicay] and FTC/TAF tablets)	TAF is available only as FTC/TAF in FDC (Descovy); not available as an individual drug. See Tenofovir Alafenamide.

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

Preferred Initial Regimens and ARV Drugs Based on Age and Weight at Time of Treatment Initiation 8C. Children Aged ≥2 Years to <12 Years			
Panel Recommendation[a,b]	**Regimen or ARV Drug**	**Age and/or Weight Restriction[c]**	**Formulations and Comments[c]**
Alternative anchor drugs in an ART regimen with a *Preferred* NRTI backbone **for children aged ≥2 years to <12 years[i]**	• ATV powder plus RTV powder (boosted PI)	≥15 kg to ≤ 25 kg	ATV is available in 50-mg powder packets; RTV is available in 100-mg powder packets.
	• ATV capsules plus RTV tablets (boosted PI)	≥15 kg	ATV and RTV powder can be mixed with soft food or liquid.
	• ATV plus COBI in FDC tablet (ATV/c, boosted PI)	≥35 kg	
	• DRV plus RTV (boosted PI)	≥20 kg	DRV is available in an oral solution or tablets to be taken with RTV powder or tablets.
	• DRV plus COBI in FDC tablet (DRV/c, boosted PI)	≥25 kg	
	• NVP	None	NVP is available in an oral solution or immediate-release tablets.
	• NVP XR	Aged ≥6 years	
	• EFV	Aged ≥3 years and ≥10 kg	EFV capsules can be opened and used as a sprinkle formulation for children who are unable to swallow pills.
	• DOR	≥35 kg	DOR is available as a single-tablet regimen (DOR/3TC/TDF).

[a] Panel recommendations summarized in this table are for children with HIV-1 infection.

[b] Recommendations for ARV drugs or ART regimens to be used in special circumstances are addressed in the text (e.g., ARV resistance, HBV coinfection).

[c] Additional information about FDCs is available in Appendix A. Pediatric Antiretroviral Drug Information, Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class, and Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents.

[d] ABC is not approved by the 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 result should be available. An FDC tablet that contains ABC/3TC (generic) is available for use in children weighing ≥25 kg.

[e] If DTG dispersible tablets are not available, RAL can be administered using either the oral granules for suspension dispersed in water or the chewable tablets dispersed in juice, formula, or milk.

Table 8. Antiretroviral Treatment Regimens Recommended for Initial Therapy for HIV Infection in Infants and Children: Birth to <12 Years of Age

[f] An NRTI backbone of ZDV plus 3TC twice daily or ABC plus 3TC twice daily allows for all medications to be administered at the same time when given in combination with LPV/r or RAL. There is considerable experience with ZDV and 3TC in this age group. ABC is associated with less bone marrow toxicity than ZDV and may be the preferred NRTI for long-term use.

[g] BIC/FTC/TAF tablets are available in two different strengths, with the lower-strength tablet for children weighing ≥14 kg and <25 kg.

[h] The product label for BIC/FTC/TAF (Biktarvy) states that for children who are unable to swallow a whole tablet, the BIC/FTC/TAF tablet can be split and each part taken separately, as long as all parts are ingested within approximately 10 minutes.

[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. 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.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DTG = dolutegravir; EFV = efavirenz; FDA = U.S. Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; HBV = hepatitis B virus; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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

See Appendix A. Pediatric Antiretroviral Drug Information and Table 7. Antiretroviral Regimen Considerations for Initial Therapy Based on Specific Clinical Scenarios in the Adult and Adolescent Antiretroviral Guidelines for more information. For detailed information about drug interactions, see Drug–Drug Interactions and ARV class-specific tables 24a to 24g and 25a to 25b in Adult and Adolescent Antiretroviral Guidelines, as well as the HIV Drug Interaction Checker and updated prescribing information.

Note: Drugs within each ARV class are listed in alphabetical order.

ARV Class/ Agent(s)	Advantages	Disadvantages
All INSTIs	**INSTI Class Advantages** • Well tolerated	**INSTI Class Disadvantages** • Possible weight gain in adults, especially Black/African American women • The potential exists for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4, UGT1A1). Information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker. • Oral absorption can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations.
BIC	• Once-daily administration • No food requirement • Coformulated with TAF/FTC (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class) • Higher barrier to resistance than RAL	• The FDC tablet **is not recommended** for patients with hepatic impairment or an estimated CrCl <30 mL/min. • CNS side effects, particularly sleep disturbances. Depression and suicidal ideation (rare; usually in people with preexisting psychiatric conditions). • CYP3A4 and UGT1A1 substrate (but not a CYP3A4 inducer or inhibitor); potential for drug–drug interactions. • Inhibits tubular secretion of creatinine, resulting in an increase in serum creatinine without affecting glomerular function. This increase is generally benign but can be misinterpreted by clinicians not aware of this side effect. Added follow-up may be required in patients with underlying renal disease.

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

ARV Class/ Agent(s)	Advantages	Disadvantages
DTG	• Daily dosing after the first 2 weeks of life (Note: every other day dosing during first 2 weeks of life). No food requirement. • Coformulated with ABC/FTC and with 3TC (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class). • 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. • Higher barrier to resistance than RAL.	• UGT1A1 substrate; potential for drug–drug interactions. • CNS side effects, particularly sleep disturbances. Depression and suicidal ideation (rare; usually in people with preexisting psychiatric conditions). • Inhibits tubular secretion of creatinine, resulting in an increase of serum creatinine without affecting glomerular function. This increase is generally benign but can be misinterpreted by clinicians not aware of this side effect. Added follow-up may be required in people with underlying renal disease. • Every other day dosing during the first 2 weeks of life may be challenging for some caregivers.
RAL	• No food requirement. • Available in tablet, chewable tablet, and oral granules for suspension formulations. • Chewable tablets can be crushed and mixed with various liquids for infants aged ≥4 weeks who weigh ≥3 kg. • Favorable lipid profile.	• Lower barrier to resistance than boosted PI-, BIC-, or DTG-based regimens. • Oral absorption of RAL can be reduced by simultaneous administration with drugs or supplements containing polyvalent cations. • UGT1A1 substrate; potential for drug interaction. • Depression and suicidal ideation (rare; usually in patients with preexisting psychiatric conditions). • Increases in creatine kinase, myopathy, and rhabdomyolysis have been reported. • 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. • Higher pill burden than other INSTI-based regimens. No FDC formulation.
All NNRTIs	**NNRTI Class Advantages** • Longer half-life allows for once-daily dosing of DOR, EFV, and RPV • Lower risk of dyslipidemia and fat maldistribution than PIs • PI-sparing	**NNRTI Class Disadvantages** • Prevalence of NNRTI-resistant viral strains in patients who have never used ART drugs and the drugs' low barrier for the development of resistance. A single mutation can confer resistance, with cross-resistance between EFV and NVP.

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

ARV Class/ Agent(s)	Advantages	Disadvantages
	• Lower pill burden than PIs for children taking the solid formulation; easier to use and adhere to than PI-based regimens	• Rare but serious and potentially life-threatening cases of skin rash (including SJS) and hepatic toxicity are possible. 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 Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.
DOR	• Once-daily administration • Available as a single-drug tablet and coformulated with TDF/FTC (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class) • No food requirement • Has continued antiviral activity in the setting of some NNRTI mutations • Favorable lipid profile • Not associated with weight gain compared with boosted DRV or EFV	• Neuropsychiatric AEs, but fewer than reported for EFV. • DOR is contraindicated when coadministered with drugs that are strong CYP3A4 enzyme inducers (see Doravirine). • Potential for CYP3A4 drug interactions. • Treatment-emergent DOR resistance mutations may confer resistance to certain NNRTIs.
EFV	• Once-daily administration. • Available as a single-drug tablet and coformulated with TDF/FTC and TDF/3TC (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class). • Can give with food (but avoid high-fat meals); usually recommended to be taken on an empty stomach. • Capsules can be opened and added to food.	• CNS side effects, including dizziness, abnormal dreams, headache, depression, suicidality, insomnia, and somnolence. Bedtime dosing is recommended to reduce CNS effects. • Rash (generally mild); QTc prolongation, dyslipidemia. • Potential for CYP3A4 drug interactions. • No commercially available liquid formulation. • Limited data on dosing for children aged <3 years. • No data on dosing for children aged <3 months.

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

ARV Class/ Agent(s)	Advantages	Disadvantages
NVP	• Liquid formulation is available. • Dosing information for young infants is available. • No food requirement • Extended-release formulation that allows once-daily dosing in older children is available.	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Twice-daily dosing necessary in children with body surface area <0.58 m^2 • Low barrier to resistance
RPV	• Once-daily dosing • Available as a single-drug tablet and coformulated with TDF/FTC and TAF/FTC (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class)	• Should not use in children with viral loads >100,000 copies/mL. • Food requirement. Must be taken with a ≥500 kcal meal at a consistent time each day; this may affect adherence. • Potential for CYP3A4 drug interactions. • RPV oral absorption is reduced with increased gastric pH. Use of RPV with PPIs is contraindicated; see Adult Drug–Drug Interactions for dosing recommendations when RPV is coadministered with H2 blocker or antacids. • Low barrier to resistance. • Side effects include depression, headache, skin rash, and QTc prolongation.
All PIs	**PI Class Advantages** • NNRTI-sparing. • Clinical, virologic, and immunologic efficacy are well documented. • Higher barrier to resistance than NNRTIs and RAL. 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); information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker. • Higher pill burden than NRTI-based or NNRTI-based regimens for people taking solid formulations.

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

ARV Class/ Agent(s)	Advantages	Disadvantages
		• Poor palatability of liquid preparations, which may affect adherence. • Most PIs require RTV or COBI boosting, resulting in drug–drug interactions that are associated with RTV or COBI.
ATV/r and ATV/c Unboosted ATV	• Once-daily dosing. • Powder formulation is available for young children. • 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. • Food requirement. • Indirect hyperbilirubinemia is common but asymptomatic. Scleral icterus may be distressing to the patient, which may affect adherence. Other side effects include cholelithiasis, nephrolithiasis, and PR interval prolongation. • Must be used with caution in patients with preexisting conduction system defects (can prolong the PR interval of an ECG). • ATV boosted with RTV or COBI is recommended. Both RTV and COBI are associated with a large number of drug–drug interactions. CYP3A4 substrate and inhibitor. • ATV absorption is reduced when ATV is given with acid-lowering therapies. • COBI inhibits active tubular secretion of creatinine and can increase serum creatinine without affecting renal glomerular function. This increase is generally benign but can be misinterpreted by clinicians not aware of this side effect. Added follow-up may be required in individuals with underlying renal disease.
DRV/c or DRV/r	• Can be used once daily in children aged ≥12 years. • Liquid formulation is available. • DRV requires a boosting agent. • Available as a single-drug tablet and coformulated as DRV/c and DRV/c/TAF/FTC (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class).	• Pediatric pill burden high with current tablet dose formulations. • Food requirement. • Must be boosted with RTV or COBI to achieve adequate plasma concentrations. • Contains sulfa moiety; the potential for cross-sensitivity between DRV and other drugs in sulfonamide class is unknown. Other side effects include hyperlipidemia and increased transaminases. • RTV and COBI are associated with a large number of potential drug–drug interactions.

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

ARV Class/ Agent(s)	Advantages	Disadvantages
		• COBI inhibits active tubular secretion of creatinine and can increase serum creatinine without affecting renal glomerular function. This increase is generally benign but can be misinterpreted by clinicians not aware of this side effect. Added follow-up may be required in patients with underlying renal disease. • Can be used only once daily in the absence of certain PI-associated resistance mutations.
LPV/r	• LPV is 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–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 preexisting conduction system defects (can prolong PR and QT interval of an ECG).
ABC plus (3TC or FTC)	• Palatable liquid formulations • No food requirement • Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class)	• Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC. • ABC use has been associated with CV disease and cardiac events in some, but not all, observational studies conducted in adults.
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 or as a Co-packaged Formulation, by Drug Class) • Active against HBV; a recommended dual-NRTI option for individuals with HBV/HIV coinfection	• Limited data on the safety and efficacy of this combination in children • Increased lipid levels

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

ARV Class/ Agent(s)	Advantages	Disadvantages
TDF plus (3TC or FTC)	• Once-daily dosing for TDF. • Resistance is slow to develop. • Lower risk of mitochondrial toxicity than other NRTIs. • No food requirement. • TDF is 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 or as a Co-packaged Formulation, by Drug Class). • Active against HBV; a recommended dual-NRTI option for individuals with HBV/HIV coinfection.	• Limited pediatric experience • Potential bone and renal toxicity
ZDV plus (3TC or FTC)	• Extensive pediatric experience • Coformulations of ZDV and 3TC are available for children weighing ≥30 kg. • Palatable liquid formulations • No food requirement • 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.

Key: 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; 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; PPI = proton pump inhibitor; PR interval = interval between the onset of atrial depolarization to the onset of ventricular depolarization; QTc interval = duration of ventricular electrical activity, measured as the time between the start of the QRS complex and the end of the T wave, corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TG = triglyceride; ZDV = zidovudine

What Not to Start: Regimens Not Recommended for Initial Antiretroviral Therapy in Infants and Children

The Panel classifies ARV drugs and drug combinations that are not recommended for use in ARV-naive children into one of two categories:

Not Recommended for Initial Therapy: These include ARV drugs and drug combinations that are not recommended for initial ART regimens in children because they produce an inferior virologic response, they pose potential serious safety concerns (including potentially overlapping toxicities), they are associated with pharmacologic antagonism, or better options are available within a drug class.

Insufficient Data to Recommend for Initial Therapy: ARV drugs and drug combinations that are approved for use in adults but have insufficient, limited, or no PK and/or safety data for children cannot be recommended for initial therapy in children. However, on occasion, these drugs and drug combinations may be appropriate to consider when managing treatment-experienced children (see Management of Children Receiving Antiretroviral Therapy).

When a health care provider needs to start an ARV regimen that is not a *Preferred* or *Alternative* regimen in age- and weight-appropriate categories recommended in the What to Start section, additional information and guidance can be obtained from the individual drug sections in the Pediatric Antiretroviral Guidelines. To further assist health care providers, ARV drugs that are not recommended by the Panel for initial therapy in children who are ARV-naive are listed in Table 10 below.

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

ARV Regimen	Rationale
Regimens containing only **NRTIs, such as a single NRTI, two NRTIs, or three NRTIs (including nucleotide RTIs, TDF, TAF)**	Inferior virologic efficacy, with high rates of early viral failure
Regimens containing three drug classes	Potential to induce multiclass resistance. Use as an initial regimen in children has not been studied.
Regimens containing three **NRTIs** and one **NNRTI**	Added cost and complexity outweigh any benefit
Dual NNRTI combinations	Enhanced toxicity
Dual-**PI** regimens	Insufficient data to recommend; potential for added toxicities
Oral regimens containing only two ARV drugs	Not FDA approved for pediatric use. For ARV-naive adolescents ≥12 years of age who weigh ≥25 kg and meet criteria listed above in Recommended Regimens for Children and Adolescents Aged ≥12 Years, a combination of DTG/3TC can be used as an alternate regimen for initial therapy.
Use of TAF/FTC or TDF/FTC with COBI or RTV boosted PIs in children <35 kg	The COBI or RTV component will also increase tenofovir exposure and no data is available for the use of these combinations
ARV Component	**Rationale**
Any regimen containing 3TC and FTC	Similar resistance profile and no additive benefit
Any regimen containing TDF and TAF	No data to suggest potentially additive efficacy
Unboosted **ATV-**containing regimens in children	Inadequate drug exposure
CAB	Not FDA approved for use in individuals who are ARV-naive or in children aged <12 years and weighing <35 kg
DRV/r in children <3 years	Potential for seizures
Once-daily **DRV-**based regimens in children aged ≥3 years to <12 years	Insufficient data to recommend
EFV-based regimens for children aged <3 years	CYP2B6 genotyping required to determine appropriate dosing
ETR-based regimens	Insufficient data to recommend; unlikely to be used as initial therapy

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

EVG-based regimens	First-generation INSTIs with lower barriers to resistance than second-generation INSTIs (BIC and DTG) that are now available for initial ARV regimens in children
FTR	Not FDA approved for use in adults who are ARV-naive or for pediatric use
IBA	Not FDA approved for use in adults who are ARV-naive or for pediatric use
LEN	Not FDA approved for use in adults who are ARV-naive or for pediatric use
LPV/r dosed once daily	Inadequate drug exposure
MVC-based regimens	Only effective for CCR5-tropic virus
TDF-containing regimens in children aged <2 years	Potential bone toxicity. Appropriate dose has yet to be determined.
NVP as a component of initial ARV regimen in adolescent girls with CD4 count >250 cells/mm^3 and adolescent boys with CD4 count >400 cells/mm^3	Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in the patient group

Key: ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; CYP = cytochrome P450; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FDA = U.S. Food and Drug Administration; FTR = fostemsavir; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

Knowledge Gaps

- Studies are needed to sufficiently inform clinical guidelines and recommendations for the use of currently approved ARV agents in HIV treatment and HIV prophylaxis (in the perinatal period) in preterm and low-birth-weight newborns. PK studies on the use of integrase inhibitors in this population are particularly needed.
- Research is needed that provides more information on safe and effective options for simplifying treatment regimens in infants and young children with HIV, particularly those aged <2 years. Such options may include FDC or novel, more palatable ways to administer the ARV medications currently available for this population (e.g., dispersible tablets, films that allow direct oral administration).
- Studies are needed that explore the effectiveness and safety considerations of LA injectable ARVs for HIV treatment of children aged <12 years and weighing <35 kg. When LA ARV drugs are approved for this population, implementation research will be needed to explore benefits and barriers to the delivery of these injectables at home by trained caregivers. This work will leverage existing adolescent and adult guidelines and generate pediatric-specific data.

- Translational research is needed to provide more information on drugs with different mechanisms of action in pediatric populations. Examples include the development of potent anti-HIV-1 broadly neutralizing antibodies for the prophylaxis and treatment of HIV and the development of HIV-1 vaccines both for prophylaxis and treatment of HIV in different age groups, including HIV-exposed newborns, neonates, infants, children, and young adolescents.
- Studies are needed to support the development, optimization, and validation of new methods of laboratory testing to allow the safe use of ARV agents in preterm and low-birth-weight neonates in high-resource countries. For example, studies exploring ways to measure binding of ARV agents to albumin would provide valuable insights for pediatric HIV medicine.

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