Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

Developed by the HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Pediatric Guidelines:

Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv. Accessed (insert date) [include page numbers, table number, etc., if applicable].

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinical Info website (https://clinicalinfo.hiv.gov/).

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What's New in the Guidelines

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has reviewed the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* and revised the text and references where indicated. Key updates are summarized below.

April 11, 2022

The U.S. Food and Drug Administration (FDA) recently approved long-acting injectable cabotegravir and rilpivirine (Cabenuva) for use in children and adolescents aged ≥12 years and weighing ≥35 kg. This change has been incorporated in the Cabotegravir and Rilpivirine drug sections; other sections have not been updated yet. The Panel has not made revisions to address the recent FDA approval of the dispersible table formulation of the fixed-dose combination (FDC) of abacavir/dolutegravir/lamivudine (Triumeq PD) for use in children weighing 10 kg to 25 kg; this will be addressed in a future update.

Clinical and Laboratory Monitoring of Pediatric HIV Infection

- Some updates were made for clarification and to align content in bulleted recommendations, text, and Table 5. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy.
- Some experts would consider monitoring HgbA1C in children at risk for prediabetes/diabetes, rather than routine blood glucose.
- The Panel added a statement to point out that periodic measurements of body weight—important for dose modification in the rapidly growing infant and to monitor for excessive weight gain as a possible adverse effect of some antiretroviral (ARV) drugs—are not possible with telemedicine visits.
- The Panel also noted that children with HIV who are relocating from outside the United States may benefit from thyroid function studies and additional evaluations, such as screening for tuberculosis, gastrointestinal parasites, hepatitis infection, and lead level.

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

- The Panel has updated its recommendations for several drugs following recent FDA approvals of new pediatric dosing strength formulations for bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF, Biktarvy) and emtricitabine/tenofovir alafenamide (FTC/TAF, Descovy) and the approval of doravirine (DOR) and doravirine/emtricitabine/tenofovir disoproxil fumarate (DOR/FTC/TDF, Delstrigo) for pediatric use.
    - The Panel now recommends BIC/FTC/TAF as a *Preferred* integrase strand transfer inhibitor (INSTI)–based regimen for children aged ≥2 years and weighing ≥14 kg **(AI*).** Previously, this regimen was limited to use in children aged ≥6 years and weighing ≥25 kg.

- DOR plus a two-nucleoside reverse transcriptase inhibitor (NRTI) backbone is now recommended as an *Alternative* non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimen for children and adolescents weighing ≥35 kg **(BI*).** The Panel's recommendation is supported by data from studies that evaluated the efficacy and tolerability of this drug in adults, as well as early findings from pediatric pharmacokinetic (PK) studies. DOR is also available in a FDC tablet as DOR/FTC/TDF (Delstrigo).
- FTC/TAF (Descovy) is recommended as a *Preferred* dual-NRTI combination in children and adolescents weighing ≥14 kg when used with an INSTI or NNRTI. Use of Descovy with an INSTI or NNRTI was previously limited to children weighing ≥25 kg.

- The Panel recommends abacavir (ABC) plus lamivudine (3TC) or FTC as a *Preferred* dual-NRTI combination in children aged ≥3 months **(AI)** and now recommends it from birth in full-term infants aged <3 months **(BIII).** A negative test for the HLA-B5701 allele should be obtained before starting ABC, regardless of age. Previously, the Panel recommended ABC for infants aged ≥1 month. The Panel changed its recommendation based on PK modeling of neonatal ABC dosing to target adult plasma ABC exposures and on observational data supporting safety of ABC in full-term neonates aged <1 month. An ABC dosing recommendation based on PK simulation models has been endorsed by the World Health Organization using weight-band dosing for full-term infants from birth to 1 month of age. The FDA has approved ABC for use in children aged ≥3 months.

What Not to Start: Regimens Not Recommended for Use in Antiretroviral-Naive Children

- The section text and Table 9. Antiretroviral Regimens or Components That Are Not Recommended for Initial Treatment of HIV Infection in Children and Adolescents have been updated to include two-drug ARV regimens, as well as three drugs that are not FDA approved for use in ARV-naive children or adults: cabotegravir, fostemsavir, and ibalizumab.
- Any ARV regimen containing both TDF and TAF has been added to Table 10. Antiretroviral Regimens or Components That Are Never Recommended for Treating HIV in Children and Adolescents.

Special Considerations for Antiretroviral Therapy Use in Adolescents with HIV

- This section has been updated to include additional content about substance use concerns in adolescents.

Adherence to Antiretroviral Therapy in Children and Adolescents with HIV

- This section has been revised to provide recent data about the following adherence interventions: smartphone-based reminders, peer support interventions, modified directly administered ARV therapy, and a multicomponent intervention—including remote coaching, electronic dose monitoring, and tailored outreach.

Management of Medication Toxicity or Intolerance

- The Tables for Antiretroviral Therapy–Associated Adverse Effects and Management have been updated. Recommendations have been reviewed with updates regarding associated ARVs, onset and clinical manifestations, estimated frequency, risk factors, prevention and monitoring, and management where indicated.

- Table 15a. Central Nervous System Toxicity
- Table 15b. Dyslipidemia
- Table 15c. Gastrointestinal Effects
- Table 15d. Hematologic Effects
- Table 15e. Hepatic Events
- Table 15f. Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus
- Table 15g. Lactic Acidosis
- Table 15h. Lipodystrophies and Weight Gain
- Table 15i. Nephrotoxic Effects
- Table 15j. Osteopenia and Osteoporosis
- Table 15k. Rash and Hypersensitivity Reactions

Management of Children Receiving Antiretroviral Therapy

- The sections on Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy and Recognizing and Managing Antiretroviral Treatment Failure have been updated to incorporate the most recent ARV options based on recent FDA approvals of drugs for pediatric use and changes to Panel recommendations for the use of ARV drugs. This information is summarized under the headings for What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children and Appendix A: Pediatric Antiretroviral Drug Information.

Appendix A: Pediatric Antiretroviral Drug Information

Drug sections and FDC Table 1 and Table 2 in this appendix were reviewed and updated to include recent pediatric data and dosing and safety information, plus FDA approvals of new formulations and FDCs. Significant changes are summarized below:

- Although ABC is not approved by the FDA for use in infants aged <3 months, the Abacavir section has been updated to include a dosing recommendation for full-term infants aged <1 month. The Panel's recommendation is based on data from PK modeling of neonatal ABC dosing to target adult plasma ABC exposures and on observational data supporting safety of ABC in full-term neonates aged <1 month. The Panel has also revised its previous dosing recommendation for full-term infants aged ≥1 month to <3 months based on modeling data provided by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1106 study and two observational cohorts.
- The Bictegravir, Emtricitabine, and Tenofovir Alafenamide sections have been updated to incorporate FDA approval of a new pediatric dosing strength for Biktarvy (BIC 30 mg/FTC 120 mg/TAF 15 mg) for use in children aged ≥2 years and weighing ≥14 kg to <25 kg.

- The Emtricitabine and Tenofovir Alafenamide sections have been updated to incorporate FDA approval of a new pediatric dosing strength for Descovy (FTC 120 mg/TAF 15 mg) for use in children weighing ≥14 kg to <25 kg.
- The Doravirine, Lamivudine, and Tenofovir Disoproxil Fumarate sections have been updated following the FDA approval of DOR and the FDC tablet DOR/3TC/TDF (Delstrigo) for use in children and adolescents weighing ≥35 kg who are ARV-naive or have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR or to the individual components of Delstrigo.
- The Cabotegravir and Rilpivirine sections have been revised to incorporate the FDA approval of the long-acting injectable regimen, Cabenuva (co-packaged cabotegravir [CAB] and rilpivirine [RPV] suspensions), for treatment of HIV in children and adolescents aged ≥12 years and weighing ≥35 kg with HIV RNA levels <50 copies/mL on a stable ARV regimen, no history of treatment failure, and no known or suspected resistance to CAB or RPV. The FDA has also approved the oral formulation of CAB (Vocabria) for this group of children and adolescents. Oral lead-in dosing of CAB and RPV is now an option, rather than a requirement, when starting Cabenuva; patients may proceed to Cabenuva directly from their current ARV regimen.
- In the Efavirenz (EFV) section, the Panel has added a recommendation to measure vitamin D in children receiving EFV and to prescribe vitamin D supplementation for those with vitamin D deficiency (see Table 15j. Osteopenia and Osteoporosis for additional information). This recommendation is based on studies in adults showing that use of EFV is associated with low vitamin D levels, as well as studies that have found an association between EFV use and low bone mineral density.
- Some text was removed from the Lopinavir/Ritonavir (LPV/r) section to clarify that the Panel does not endorse use of LPV/r in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days due to the risk of metabolic and cardiac toxicity.
- The Panel has revised the Nevirapine (NVP) section to include dosing recommendations for preterm infants at a gestational age of 32 weeks to <34 weeks based on review of PK modeling and simulation data. This dosing strategy has not been evaluated in clinical trials and is not approved by the FDA. Previously, the Panel's dosing recommendations for preterm infants were limited to a gestational age of 34 weeks to <37 weeks.

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Updated: Dec.30, 2021
Reviewed: Dec.30, 2021

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Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

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Key: C = Chair; CC = Co-Chair; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; HHS = Member from the Department of Health and Human Services; M = Member; N/A = Not Applicable; NVO = Non-Voting Observer

Introduction

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (Pediatric Guidelines) address the diagnosis of HIV infection in infants and children and the use of antiretroviral therapy (ART) in children with HIV, including adolescents with sexual maturity ratings (SMRs, formerly Tanner staging) 1 to 3. Note that the guidelines developed by the Panel on Antiretroviral Guidelines for Adults and Adolescents are suitable for the care and management of adolescents in late puberty (SMRs 4–5).

The Pediatric Guidelines also include recommendations for managing adverse events that are associated with the use of antiretroviral (ARV) drugs in children and a detailed review of information about the safety, efficacy, and pharmacokinetics (PKs) of ARV agents in children. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel), a working group of the Office of AIDS Research Advisory Council (OARAC), reviews new data on an ongoing basis and regularly updates the guidelines. The guidelines are available on the Clinical Info website.

The Clinical Info website also provides separate guidelines for the following:

- The prevention and treatment of opportunistic infections (OIs) in children who were exposed to HIV and children with HIV infection[1];
- The use of ARV drugs in adolescents and adults with HIV[2];
- The use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States[3];
- The prevention and treatment of OIs in adolescents and adults with HIV[4]; *and*
- Other federally approved medical practice guidelines for HIV/AIDS are available, including HIV Counseling, Testing, and Referral; Hormonal Contraception; Laboratory Testing; Prevention with Persons with HIV; Occupational Postexposure Prophylaxis (PEP); Nonoccupational Postexposure Prophylaxis (nPEP); Pre-exposure Prophylaxis (PrEP); and Caring for Persons with HIV in Disaster Areas. In 2020, Guidance for COVID-19 and Persons with HIV was added.

These guidelines are developed for the United States and may not be applicable in other countries. The World Health Organization provides guidelines for resource-limited settings.

The Pediatric Guidelines and the Perinatal Guidelines contain some closely related content that can overlap. To ensure that information is consistent across the guidelines and that users can easily find the information they need, the Panels that publish these two sets of guidelines have developed a process to jointly produce sections for shared content areas. The development of these sections is led by a group composed of members from both Panels; the sections are discussed separately and voted on by each full Panel. Jointly produced sections include—

- Maternal HIV Testing and Identification of Perinatal HIV Exposure
- Diagnosis of HIV Infection in Infants and Children
- Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection

Since the guidelines were first developed in 1993 (with the support of the François-Xavier Bagnoud Center, Rutgers, The State University of New Jersey), advances in medical management have dramatically reduced both the number of new pediatric HIV infections and the morbidity and mortality in children with HIV in the United States. The widespread use of ARV drugs in people with HIV during pregnancy and the use of ARV prophylaxis in infants who have been exposed to HIV have reduced the annual rate of perinatally acquired HIV infection[5,6] from a peak of 43.1 per 100,000 births in 1992 to 0.8 per 100,000 births in 2019. Racial and ethnic disparities are evident in annual rates of new perinatal infection; in 2019, perinatal infections occurred in Black or African American infants (2.9 per 100,000 births) at annual rates of 5 and 10 times that of Hispanic/Latinx (0.6 per 100,000 births) and White infants (0.3 per 100,000 births), respectively.[5] Since the introduction of ART, mortality in children with perinatal HIV infection has decreased by about 90%, and the incidence of OIs and other infections in these children has significantly declined.[7,8] Children with HIV are less likely to develop AIDS because of routine and early initiation of effective ART.[9-11] ARV drug-resistance testing has made it easier for clinicians to choose effective initial and subsequent regimens. Treatment strategies focus on timely initiation of ARV regimens that are capable of maximally suppressing viral replication, which can prevent disease progression, preserve or restore immunologic function, and prevent the development of drug resistance. In addition, the availability of new drugs and drug formulations has led to more potent regimens with lower toxicity, lower pill burden, and less frequent medication administration—all factors that can improve adherence and outcomes. However, delays in the development and testing of pediatric formulations continue to limit the availability of optimal ARV regimens for children, especially infants.[12]

Children with HIV in the United States are increasingly born outside the United States[13]; they may be members of immigrant families or they may have been adopted by U.S. residents. These children may have non-B subtypes of HIV, incomplete medical and treatment histories, an increased risk of tuberculosis and other infections that are endemic in their countries of origin, and legal and psychosocial needs related to immigration.

Finally, as children with HIV grow older, new challenges arise related to adherence, drug resistance, reproductive health planning, transition to adult medical care, and the potential for long-term complications from HIV and its treatments.[11,14,15]

The pathogenesis of HIV infection and the virologic and immunologic principles underlying the use of ART are generally similar for all individuals with HIV. However, unique considerations exist for infants, children, and adolescents with HIV, including—

- Acquisition of infection through perinatal exposure for most children with HIV;
- *In utero* and neonatal exposure to ARV drugs in most children with perinatal HIV infection[16];
- The need to use HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months;
- Age-specific interpretations of CD4 T lymphocyte (CD4) cell counts;
- Higher plasma viral loads in infants with perinatal HIV infection than in adolescents and adults with nonperinatal HIV infection;
- Age-related changes in PK parameters that are caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance[17];
- Differences in the clinical manifestations and treatment of HIV in growing, immunologically immature individuals; *and*

- Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

The care of children with HIV is complex and evolves rapidly as results of new research are reported, new ARV drugs are approved, and new approaches to treatment are recommended. As new drugs become available, a critical need exists for clinical trials that define appropriate drug doses and identify possible toxicities in infants, children, and adolescents. As additional ARV drugs are approved and optimal strategies for the use of these drugs in children become better understood, the Panel will modify these guidelines.

The recommendations in these guidelines are based on the current state of knowledge regarding the use of ARV drugs in children. Evidence is drawn primarily from published data regarding the treatment of HIV in infants, children, adolescents, and adults; however, when no such data are available, unpublished data and the clinical expertise of the Panel members are also considered. These guidelines are only a starting point for medical decision-making and are not meant to supersede the judgment of clinicians who are experienced in the care of children with HIV. Because of the complexity of caring for children with HIV, health care providers with limited experience in the care of these patients should consult a pediatric HIV specialist. The HIV/AIDS Management Clinician Consultation Center is an excellent resource for telephone consultation. The Center can be contacted at 1-800-933-3413, 9 a.m. to 8 p.m. ET, Monday through Friday.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	The guidelines provide guidance to HIV care practitioners in the United States on the optimal use of antiretroviral (ARV) agents when treating infants, children, and adolescents in early to mid-puberty (sexual maturity rating [SMR] 1–3) with HIV.
Panel Members	The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) is composed of approximately 34 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection (e.g., parents and caregivers of children and youth with HIV). The Panel also includes at least one representative from each of the following Department of Health and Human Services (HHS) agencies: the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Paediatric and Perinatal HIV/AIDS Research Group and a representative from the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine participate as nonvoting, *ex officio* members of the Panel. The U.S. government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the panel roster.
Financial Disclosure	All members of the Panel submit an annual financial disclosure statement in writing, reporting any association with manufacturers of ARV drugs or diagnostics used to manage HIV infections. A list of the latest disclosures is available on the Clinical Info website.
Users of the Guidelines	Providers of care to infants, children, and adolescents with HIV in the United States
Developer	Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of the Office of AIDS Research Advisory Council (OARAC)

Topic	Comment
Funding Source	Office of AIDS Research, NIH, and HRSA
Evidence Collection	A standardized review of recent, relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel working groups. The recommendations generally are based on studies published in peer-reviewed journals. The Panel may occasionally use unpublished data to revise the guidelines, particularly when the new information relates to dosing or patient safety. These data come from presentations at major conferences or from the FDA and/or drug manufacturers.
Recommendation Grading	Described in Table 2
Method of Synthesizing Data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version that is acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations.
Other Guidelines	These guidelines focus on infants, children, and adolescents in early-to-mid-puberty (SMR 1–3) with HIV. Guidelines for the treatment of adolescents in late puberty (SMR 4–5) are provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents. Separate guidelines outline the use of antiretroviral therapy (ART) in people who are pregnant or are trying to conceive (including maternal and infant interventions to prevent perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These and other HIV guidelines are also available on the Clinical Info website.
Update Plan	The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the Clinical Info website until the guidelines can be updated with appropriate changes. All sections of the guidelines are reviewed at least once a year, with updates as appropriate.
Public Comments	A 2-week public comment period follows the release of the updated guidelines on the Clinical Info website. The Panel reviews these comments to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at Contact Us

Basis for Recommendations

Recommendations in these guidelines are based on scientific evidence and expert opinion. Each recommendation includes a letter (**A**, **B**, or **C**) that represents the strength of the recommendation and a Roman numeral (**I**, **II**, or **III**) that represents the quality of the evidence that supports the recommendation.

When approving drugs for use in children, the FDA often extrapolates efficacy data from adult trials, in addition to using safety and PK data from studies in children. Because of this, recommendations for use of ARV drugs in children often rely, in part, on data from clinical trials or studies in adults. Because the course of HIV disease and the effects of ARV drugs in pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients, it is appropriate to base approval of ARV drugs for children on evidence from adequate and well-controlled investigations in adults if—

- Supplemental data exist on the PKs of the drug in children, indicating that systemic exposure in adults and children is similar; *and*
- Studies are provided that support the safety of using the drug in pediatric patients.[18-20]

If a concern exists that concentration–response relationships might be different in children than in adults, then pediatric drug approval should include evidence from studies that relate drug activity to drug levels (pharmacodynamic data) in children. In many cases, the evidence from studies on the use of ARV drugs in adults (especially from randomized clinical trials) is much more substantial and higher in quality than the available evidence from studies in children. Therefore, for pediatric recommendations, the following rationale has been used when the evidence from studies in children is limited or of lower quality:

Quality of Evidence Rating I—Randomized Clinical Trial Data

- Quality of Evidence Rating I will be used if there are data from large randomized trials **in children** with clinical and/or validated laboratory endpoints.
- Quality of Evidence Rating I* will be used if there are high-quality randomized clinical trial data **in adults** with clinical and/or validated laboratory endpoints **and** pediatric data from well-designed, nonrandomized trials or observational cohort studies with clinical outcomes that are consistent with the adult studies. A rating of I* may be used for quality of evidence if, for example, a randomized Phase 3 clinical trial in adults demonstrates that a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

Quality of Evidence Rating II—Nonrandomized Clinical Trials or Observational Cohort Data

- Quality of Evidence Rating II will be used if there are data from well-designed, nonrandomized trials or observational cohorts **in children.**
- Quality of Evidence Rating II* will be used if there are well-designed, nonrandomized trials or observational cohort studies **in adults** with supporting and consistent information from smaller, nonrandomized trials or cohort studies with clinical outcome data in children. A rating of II* may be used for quality of evidence if, for example, a large observational study in adults demonstrates a clinical benefit to initiating treatment at a certain CD4 cell count, and data from smaller observational studies in children indicate that treatment initiation at a similar CD4 cell count is associated with clinical benefit.

Quality of Evidence Rating III—Expert Opinion

- The criteria do not differ for adults and children.

In an effort to improve the quality of evidence available to guide the management of HIV infection in children, clinicians are encouraged to discuss participation in trials with children and their caregivers. Information about clinical trials for adults and children with HIV can be obtained from the Clinical Info website or by telephone at 1-800-448-0440.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials **in children**[a] with clinical outcomes and/or validated laboratory endpoints **I*:** One or more randomized trials **in adults** with clinical outcomes and/or validated laboratory endpoints, plus accompanying data **in children**[a] from one or more well-designed, nonrandomized trials or observational cohort studies with clinical outcomes **II:** One or more well-designed, nonrandomized trials or observational cohort studies **in children**[a] with clinical outcomes **II*:** One or more well-designed, nonrandomized trials or observational cohort studies **in adults** with clinical outcomes, plus accompanying data **in children**[a] from one or more smaller nonrandomized trials or cohort studies with clinical outcome data **III:** Expert opinion

[a] These are studies that include children or children and adolescents, but not studies that are limited to postpubertal adolescents.

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Maternal HIV Testing and Identification of Perinatal HIV Exposure

Updated: Dec.30, 2021
Reviewed: Dec.30, 2021

Panel's Recommendations
• HIV testing is recommended as a standard of care for all sexually active people and should be a routine component of prepregnancy care **(AII).** • All pregnant people should be tested as early as possible during each pregnancy (see Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations and Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens from the Centers for Disease Control and Prevention [CDC]) **(AII).** • Partners of all pregnant people should be referred for HIV testing when their status is unknown **(AIII).** • Repeat HIV testing in the third trimester is recommended for pregnant people with negative initial HIV tests who are at increased risk of acquiring HIV, including those receiving care in facilities that have an HIV incidence of ≥1 case per 1,000 pregnant women per year, those who reside in jurisdictions with elevated HIV incidence (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings from CDC), or those who reside in states or territories that require third-trimester testing **(AII).** • Repeat HIV testing is recommended for pregnant people with a sexually transmitted infection (STI) or with signs and symptoms of acute HIV infection, or ongoing exposure to HIV, as well as referral for initiation of pre-exposure prophylaxis if HIV testing is negative **(AIII).** See Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information. • Expedited HIV testing should be performed during labor or delivery for people with undocumented HIV status and for those who tested negative early in pregnancy but are at increased risk of HIV infection and were not retested in the third trimester **(AII).** Testing should be available 24 hours a day, and results should be available within 1 hour. If results are positive, intrapartum antiretroviral (ARV) prophylaxis should be initiated immediately **(AI)**. • Pregnant people who were not tested for HIV before or during labor should undergo expedited HIV antibody testing during the immediate postpartum period (or their newborns should undergo expedited HIV antibody testing) **(AII).** • When a pregnant person has a positive HIV test result during labor and delivery or postpartum, or when a newborn's expedited antibody test is positive, an appropriate infant ARV drug regimen should be initiated immediately, and the infant should not be breastfed while awaiting the results of supplemental HIV testing **(AII).** See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for guidance. • Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII).** • HIV testing is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown to identify perinatal HIV exposure and possible HIV infection **(AIII)** (see Diagnosis of HIV Infections in Infants and Children).

__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 and adolescents, but not studies limited to post-pubertal adolescents

HIV Testing in Pregnancy

HIV infection should be identified before pregnancy (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV) or as early as possible in pregnancy. In the United States, approximately 20% to 34% of infants with perinatal HIV exposure were born to people whose HIV diagnosis was not known before pregnancy.[1] Early diagnosis provides the best opportunity to improve maternal health and pregnancy outcomes to prevent infant acquisition of HIV, to identify HIV infection, and to start therapy as soon as possible in infants who acquire HIV. Universal voluntary HIV testing is recommended as the standard of care for all pregnant people in the United States by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV and the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panels), the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force.[2-6]

All HIV testing should be performed in a manner that is consistent with state and local regulations. CDC recommends the "opt-out" approach, which is allowed in many jurisdictions and involves notifying a pregnant person that HIV testing will be performed as part of routine care unless they choose not to be tested.[3] The "opt-in" approach involves obtaining specific consent before testing, and this approach has been associated with lower testing rates.[7,8] Despite the guidelines for universal HIV screening of pregnant people, recent studies indicate that fewer than 80% of women report having been tested for HIV during pregnancy.[9,10] The mandatory newborn HIV testing approach, which has been adopted by several states, involves testing newborns with or without maternal consent. In some areas, this applies to all newborns; in others, it applies only to the infants of mothers who have declined prenatal or intrapartum testing.

Partners of pregnant people should be referred for HIV testing when their status is unknown, consistent with the 2006 CDC recommendations for HIV testing of all individuals in the United States. Testing will facilitate linkage to care if a partner is diagnosed with HIV infection. Because women are more susceptible to HIV acquisition during pregnancy and the postpartum period,[11] clinicians also can initiate a discussion about preventive interventions, including pre-exposure prophylaxis (PrEP), for a pregnant person without HIV who is at risk for acquiring HIV. See Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information.

Clinicians should assess a pregnant person's risk of acute HIV infection, particularly late in pregnancy, because people may receive a negative result for expedited or rapid HIV testing when they are in the window period (the window period lasts up to 15 days post-infection when using the combined antigen/antibody immunoassay and up to 28 days when using other assays). However, during this period, the person with acute HIV will be viremic,[12] with a high risk of perinatal transmission to the newborn. The HIV RNA assay can detect the presence of HIV as early as 10 days post-infection, so this test should be used when acute HIV infection is suspected. See Acute HIV Infection for more information.

Providers should be aware that gaps in maternal HIV testing do occur and can contribute to missed opportunities for preventing perinatal HIV transmission.[13-16] Maternal HIV testing should be performed as early as possible during pregnancy, wherever a person seeks care (including emergency departments and prenatal clinics), to avoid missed opportunities to identify pregnant people with HIV. Repeat HIV testing should be performed in the third trimester for people who are at increased risk of acquiring HIV or who are living in areas of high HIV incidence, at the time of a diagnosis of a sexually transmitted infection (STI), or when they show symptoms and signs of possible acute HIV infection. Pregnant people with unknown or undocumented HIV status who present to care in labor should be tested during delivery or as soon as possible after delivery.[13-16]

Determining antenatal maternal HIV status enables—

- People with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections;
- Initiation of treatment in the identified people to maintain and improve their health and to decrease risk of HIV transmission to their fetus or infant and their partners;[3,17,18]
- Referral of partners for testing, which allows them to initiate either treatment if the results are positive or preventive interventions, including PrEP, if the results are negative if warranted (see Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods);
- Provision of ART during pregnancy and labor and provision of an appropriate antiretroviral (ARV) drug regimen to the newborn to reduce the risk of perinatal transmission;
- Counseling of pregnant people with HIV about recommended modes of delivery based on individualized risks of perinatal transmission of HIV;[19-21]
- Counseling of pregnant people with HIV about the risks of HIV transmission through breast milk (in the United States, breastfeeding is not recommended for women with HIV [see Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed]);[22] *and*
- Early diagnostic evaluation of infants exposed to HIV (see Diagnosis of HIV Infection in Infants and Children), as well as testing of other children, to permit prompt initiation of ART and any indicated prophylaxis measures.[2,23-25]

New technology has made it possible to detect HIV earlier and has reduced the performance time for laboratory-based assays, which now can be completed in <1 hour. Accordingly, the Panels now base their recommendations for HIV testing on CDC's 2014 Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations.[26] The guidelines recommend that clinicians initiate HIV testing with an immunoassay that is capable of detecting HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen (referred to as an antigen/antibody combination immunoassay). Individuals with a reactive antigen/antibody combination immunoassay should be tested further with an HIV-1/HIV-2 antibody differentiation assay (referred to as supplemental testing). Individuals with a reactive antigen/antibody combination immunoassay and a nonreactive differentiation test should be tested with a Food and Drug Administration–approved plasma HIV RNA assay to establish a diagnosis of acute HIV infection (see CDC's Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens).

Discordant HIV testing results can be seen, requiring careful evaluation and often repeat tests. Early in HIV infection, before HIV seroconversion, the antigen-antibody screen will be negative and the HIV RNA assay will be positive. This is seen in acute infection because the HIV RNA assay is positive before the antigen/antibody screen. The test combination of a positive antigen-antibody screen, negative antibody differentiation assay, and positive HIV RNA assay also can be seen early in HIV infection because the IgG-based antibody differentiation assay is positive later in infection than the antigen capture or the IgM result in the antigen-antibody screen.

Clinicians should be aware that as more individuals undergo repeat HIV testing, the number of false-positive screens will increase. The combination of a positive antigen-antibody screen with a negative antibody differentiation assay and a negative HIV RNA assay is seen in people without HIV who have a false-positive antigen-antibody screen.

These examples should make it clear that for any positive HIV 1/2 antigen-antibody screen, an HIV RNA assay should be done because the HIV RNA assay is needed to resolve questions raised by discordant results on the antigen-antibody screen and the antibody differentiation assay.

The antigen/antibody combination immunoassay is the test of choice and can be done quickly (referred to as an expedited test), but it requires trained laboratory staff and, therefore, may not be available in some hospitals 24 hours a day. When this test is unavailable, initial testing should be performed by the most sensitive expedited or rapid test available. Every delivery unit needs to have access to an HIV test that can be done rapidly (i.e., in <1 hour) 24 hours a day. If the test result is positive, the test to confirm HIV infection should be performed as soon as possible (as with all initial assays with positive results). Older antibody tests have lower sensitivity in the context of recent acquisition of HIV than antigen/antibody combination immunoassays. Therefore, testing that follows the 2014 CDC algorithm should be considered if HIV risk cannot be ruled out. Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider.

Repeat HIV Testing in the Third Trimester

Repeat HIV testing during the third trimester, before 36 weeks gestation, is recommended (see Acute HIV Infection)[27] for pregnant people with negative results on their initial HIV antibody tests who—

- Are at high risk of acquiring HIV (e.g., those who inject drugs or have sex with people who inject drugs, those who exchange sex for money or drugs, those who are sex partners of individuals with HIV, those who have had a new sex partner or more than one sex partner during the current pregnancy,[3] or those who have a suspected or diagnosed STI during pregnancy);[28] *or*
- Are receiving health care in facilities where prenatal screening identifies one or more pregnant women with HIV per 1,000 women screened, or reside in a jurisdiction that has a high incidence

of HIV or AIDS in women between the ages of 15 and 45 years (see the 2006 CDC recommendations[a]);[3,28]

- Reside in states or territories with statutes or regulations that require third-trimester testing (Arkansas, Connecticut, Delaware, Florida, Georgia, Illinois, Louisiana, Maryland, Nevada, New Jersey, North Carolina, Tennessee, Texas, Virginia, West Virginia);[29] *or*
- Have signs or symptoms of acute HIV (e.g., fever, lymphadenopathy, skin rash, myalgia, headaches, oral ulcers, leukopenia, thrombocytopenia, elevated transaminase levels).[3,28,30-32]

In addition, third-trimester testing should be offered to pregnant people who perceive themselves as being at increased risk for HIV infection (regardless of whether or not they fit any of the above criteria). Pregnant people who decline testing earlier in pregnancy should be offered testing again during the third trimester. An antigen/antibody combination immunoassay should be used because these tests have a higher sensitivity in the setting of acute HIV infection than older antibody tests.[26,33] When acute HIV infection is suspected during pregnancy, during the intrapartum period, or while breastfeeding, a plasma HIV RNA test result should be performed in conjunction with an antigen/antibody combination immunoassay. See Acute and Recent (Early) HIV Infection in the Adult and Adolescent Antiretroviral Guidelines for more information.

Providers should be proactive in assessing a pregnant person's HIV acquisition risk and implementing third-trimester HIV retesting when indicated. A study in Baltimore found that only 28% of women were retested for HIV despite the high incidence of HIV in Maryland and a high frequency of clinical risk factors.[16] A study of data from 2007 to 2014 on children in Florida with perinatal HIV exposure found that perinatal HIV transmission was associated with poor or late prenatal care, diagnosis of maternal HIV during labor and delivery or after birth, and, in some cases, acute maternal infection (as indicated by negative results for initial tests).[34] In a more recent study from a high-prevalence area in Florida, 91.7% of women had first- or second-trimester screening and, although only 82.2% had a third-trimester test, 89.3% of those without third-trimester screening had rapid testing upon admission.[35]

Repeat HIV testing at other times during pregnancy also should be considered when clinically indicated. For example, repeat testing should be performed when a pregnant person presents with symptoms that are suggestive of an STI, a confirmed STI diagnosis, or symptoms or signs that are consistent with acute HIV infection.

HIV Testing During Labor in People with Unknown HIV Status

People in labor whose HIV status is undocumented and those who tested negative early in pregnancy but are at increased risk of HIV infection and were not retested in the third trimester should undergo expedited HIV testing to identify HIV infection in the mothers and HIV exposure in their infants. HIV testing during labor has been found to be feasible, accurate, timely, and useful both in ensuring prompt initiation of intrapartum maternal ARV for fetal/infant prophylaxis (see Intrapartum Care for

[a] In 2004, these jurisdictions included Alabama, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, New York, North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, and Virginia. Since that time, advances in HIV screening, prevention, and treatment have affected HIV diagnoses among reproductive-aged women, and some of these jurisdictions may no longer meet this incidence criterion.

People with HIV) and in developing an appropriate ARV regimen for infants who are at high risk of perinatal HIV transmission (see Table 11).[2-4,23,31,36,37]

Policies and procedures must be in place to ensure that staff are prepared to provide patient education and expedited HIV testing, that appropriate ARV drugs are available whenever needed, and that follow-up procedures are in place for people who receive an HIV diagnosis and for their infants. Testing should be available 24 hours a day and, whenever possible, results should be available within 1 hour.

If the antigen/antibody combination immunoassay is not available, initial testing should be performed by the most sensitive expedited test available.

A positive expedited HIV test result must be followed by a supplemental test.[26] Immediate initiation of maternal intravenous intrapartum zidovudine is recommended to prevent perinatal transmission of HIV pending the supplemental result (see Intrapartum Care for People with HIV).[2-4,6,23,31] Pending results of supplemental maternal testing, infants should receive an ARV regimen that is appropriate for infants who are at high risk of perinatal HIV transmission as soon as possible (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV or contact the National Clinician Consultation Center Perinatal HIV Hotline). No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay, unless acute HIV infection is suspected (see Acute HIV Infection).[26]

HIV Testing During the Postpartum Period

People who have not been tested for HIV before or during labor should be offered expedited testing during the immediate postpartum period. Maternal testing should be done using the antigen/antibody combination immunoassay to screen for established and acute HIV; results should be obtained in <1 hour. If acute HIV infection is a possibility, then a plasma HIV RNA test should be sent, as well. When mothers are unavailable for testing, their newborns should undergo expedited HIV testing.[2,23,31] Postnatal ARV drugs need to be initiated as soon as possible—ideally ≤6 hours after birth—to be effective in preventing perinatal transmission. When an initial HIV test is positive in mothers or infants, it is strongly recommended that clinicians initiate an ARV regimen that is appropriate for infants who are at high risk of perinatal HIV transmission and counsel the mothers against breastfeeding pending the results of supplemental testing, which should include a plasma HIV RNA test. Breast milk can be expressed while HIV diagnostic testing is being completed, but it should not be given to the infant until testing confirms that the mother is HIV negative (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). If supplemental test results are negative and acute HIV is excluded, infant ARV drugs can be discontinued. In the absence of ongoing maternal HIV exposure, breastfeeding can be initiated. Consultation with a pediatric HIV specialist is strongly recommended if questions remain about the potential for acute maternal infection or ongoing maternal HIV exposure.

Infant HIV Testing When Maternal HIV Test Results Are Unavailable

When maternal HIV test results are unavailable (e.g., the mother has declined testing during pregnancy or for infants and children who are in foster care) or their accuracy cannot be evaluated (e.g., for infants and children who were adopted from countries where results are not reported in English), HIV testing of these infants or children is indicated to identify HIV exposure and possible infection.[2] The choice of test will vary based on the age of the child (see Diagnosis of HIV Infection in Infants and Children). Mechanisms should be developed to facilitate prompt HIV screening for infants who have been abandoned and who are in the custody of the state.

Acute Maternal HIV Infection During Pregnancy or Breastfeeding

Women are more susceptible to HIV infection during pregnancy and the early postpartum period.[38] Risk of HIV exposure should be assessed in all people who are considering becoming pregnant, as well as in all pregnant and postpartum people who previously tested negative for HIV, including those who are breastfeeding. People with risk factors for HIV acquisition before, during, and after pregnancy should receive prevention counseling and appropriate interventions, including PrEP if indicated.[38,39] (See Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods for more information. People who have acute HIV during pregnancy or lactation have an increased risk of perinatal transmission and secondary sexual transmission of HIV (see Acute HIV Infection).[27,40-43] The antigen/antibody combination immunoassay will detect acute HIV infection earlier than other immunoassays—within approximately 15 days of acquisition. When acute HIV infection is suspected, a plasma HIV RNA test should be sent as well because virologic tests can detect the presence of HIV approximately 5 days earlier than the antigen/antibody combination immunoassay. People with possible acute HIV infection who are breastfeeding should cease breastfeeding immediately until HIV infection is confirmed or excluded.[22] Breast milk can be expressed while HIV diagnostic testing is completed. Breastfeeding can resume if HIV infection is excluded and there is no ongoing risk. Care of pregnant or breastfeeding people with acute or early HIV, and their infants, should follow the recommendations in the Perinatal Guidelines (see Acute HIV Infection and Guidance for Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed).

Other Issues

Clinicians should be aware of public health surveillance systems and regulations that may exist in their jurisdictions for reporting infants who have been exposed to HIV; this is in addition to mandatory reporting of people with HIV, including infants. Reporting infants who have been exposed to HIV allows the appropriate public health functions to be accomplished.

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Diagnosis of HIV Infection in Infants and Children

Updated: Dec.30, 2021
Reviewed: Dec.30, 2021

Panel's Recommendations

• Virologic assays (i.e., HIV RNA or HIV DNA nucleic acid tests [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged <18 months with perinatal and postnatal HIV exposure; HIV antibody and HIV antigen/antibody tests should not be used **(AII).**
• Plasma HIV RNA or cell-associated HIV DNA NATs are generally equally recommended **(AII).** However, the results of plasma HIV RNA NAT or plasma HIV RNA/DNA NAT can be affected by antiretroviral therapy (ART), or by antiretroviral (ARV) drugs administered to the infant as prophylaxis or presumptive HIV therapy.
• An assay that detects HIV non-B subtype viruses or Group O infections (e.g., an HIV RNA NAT or a dual-target total DNA/RNA test) is recommended for use in infants and children who were born to mothers with known or suspected non-B subtype virus or Group O infections **(AII).** If a mother of an infant acquired HIV outside of the United States and has had repeated undetectable HIV RNA by standard testing, consultation with a clinical virologist on more sensitive HIV nucleic acid testing may be indicated.
• Virologic diagnostic testing (see Table A below) is recommended for all infants with perinatal HIV exposure at the following ages:
  ○ 14 to 21 days **(AII)**
  ○ 1 to 2 months **(AII)**
  ○ 4 to 6 months **(AII)**
• For infants who are at high risk of perinatal HIV infection, virologic diagnostic testing is recommended at birth **(AII)** and at 2 to 6 weeks after ARV drugs are discontinued **(BII).**
• A positive virologic test should be confirmed as soon as possible by a repeat virologic test **(AII).**
• Definitive exclusion of HIV infection in non-breastfed infants is based on two or more negative virologic tests conducted after infants have completed ARV prophylaxis or presumptive HIV therapy, with one negative test obtained at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens that were obtained at age ≥6 months **(AII).**
• No additional HIV testing of any kind (e.g., HIV RNA or HIV DNA NAT, HIV antibody, HIV antigen/antibody) is needed routinely for non-breastfed infants who meet the criteria for definitive exclusion of HIV and who have had no known or suspected HIV exposure after birth.
• Infants with potential HIV exposure after birth (e.g., from breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) who are aged <18 months require additional testing using HIV RNA/DNA NAT assays to establish their HIV status. Infants aged ≥18 months who have these potential exposures require HIV antigen/antibody testing.
• Age-appropriate HIV testing also is recommended for infants and children with signs and/or symptoms of HIV, even in the absence of documented or suspected HIV exposure.
• HIV antibody (or HIV antigen/antibody) tests are recommended for diagnostic testing in children with non-perinatal exposure only or in children with perinatal exposure aged >24 months **(AII).**

- When acute HIV infection is suspected, additional testing with an HIV NAT may be necessary to diagnose HIV infection **(AII).**

Note: The National Clinician Consultation Center provides consultations on issues related to the management of perinatal HIV infection (1-888-448-8765; 24 hours a day, 7 days a week).

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

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

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

Diagnosis of HIV in Infants and Children

HIV can be diagnosed definitively by virologic testing in most non-breastfed infants with perinatal HIV exposure by age 1 to 2 months and in almost all infants with HIV by age 4 to 6 months. Antibody tests, including the antigen/antibody combination immunoassays (sometimes referred to as fourth- and fifth-generation tests), do not establish the presence of HIV in infants because of transplacental transfer of maternal HIV antibodies; therefore, a virologic test must be used.[1,2] Positive virologic tests (i.e., nucleic acid tests [NATs]—a class of tests that includes HIV RNA and HIV DNA polymerase chain reaction [PCR] assays and related RNA qualitative or quantitative assays) indicate likely HIV infection. Plasma HIV RNA or cell-associated HIV DNA NATs are generally equally recommended. However, both tests can be affected by maternal antiretroviral therapy through transplacental transfer of antiretroviral (ARV) drugs from the pregnant person to fetus or by ARV drugs administered to the infant as prophylaxis or presumptive HIV therapy. In contrast, qualitative HIV proviral DNA PCR assays from whole blood detecting cell-associated virus often are less affected by ARVs.

A positive HIV test result should be confirmed as soon as possible by repeat virologic testing, because false-positive results can occur with both RNA and DNA assays.[3] For additional information on the diagnosis of Group M non-subtype B, Group O HIV-1 infections, and HIV-2 infections, see the relevant sections below and the HIV Sequence Database. Newer real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay are better at detecting non-subtype B HIV infection and Group O strains than older RNA assays.[4-9] (See Clinical and Laboratory Monitoring of Pediatric HIV Infection.) One example is the COBAS® AmpliPrep/COBAS® TaqMan-HIV-1 qualitative test (a dual-target DNA/RNA, sometimes called total nucleic acid or TNA test), which also can identify non-subtype B and Group O infections.[10,11]

Antigen/antibody combination immunoassays that detect HIV-1/2 antibodies and HIV-1 p24 antigen **are not recommended** for diagnosis of HIV infection in infants. In the first months of life, the antigen component of antigen/antibody tests is less sensitive than an HIV NAT, and antibody tests should not be used for HIV diagnosis in infants and children <18 months of age.[12-14] Children with perinatal HIV exposure who are aged 18 to 24 months occasionally have residual maternal HIV antibodies; definitive confirmation of HIV infection in children in this age group who remain HIV antibody–positive should be based on a NAT (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations below). Diagnosis in children aged >24 months relies primarily on

HIV antibody and antigen/antibody tests (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months below).[1]

An infant who has a positive HIV antibody test but whose mother's HIV status is unknown (see Maternal HIV Testing and Identification of Perinatal HIV Exposure) should be assumed to have been exposed to HIV. The infant should undergo HIV diagnostic testing, as described in Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure below,[15] and receive ARV prophylaxis or presumptive HIV therapy as soon as possible. For ARV management of newborns who have been exposed to HIV and newborns with HIV infection (including those who do not yet have confirmed infection), see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.

Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

Confirmation of HIV infection is based on the results of positive virologic tests from two separate blood samples in infants and children younger than 18 months. Table A below summarizes the timing of recommended virologic diagnostic testing for infants based on HIV transmission risk. Infants at high risk on presumptive HIV therapy may require testing at additional time points compared to infants at low risk of transmission. The risk of transmission is determined based on whether a mother is receiving ART and virally suppressed.

HIV infection can be **presumptively** excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥2 weeks and one at age ≥4 weeks) or one negative virologic test (i.e., negative NAT [RNA or DNA]) at age ≥8 weeks, or one negative HIV antibody test at age ≥6 months.[1,15]

Definitive exclusion of HIV infection in a non-breastfed infant is based on two or more negative virologic tests (i.e., negative NATs [RNA or DNA]), one at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months.

For both presumptive and definitive exclusion of HIV infection, a child must have no other laboratory evidence (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and must not be breastfeeding. No additional HIV testing of any kind (e.g., NAT, antibody, antigen/antibody) is needed routinely for non-breastfed infants who meet the criteria for definitive exclusion of HIV and who have had no known or suspected HIV exposure after birth.

Pneumocystis jirovecii pneumonia (PCP) prophylaxis is recommended for infants with **indeterminate** HIV infection status starting at age 4 to 6 weeks until they are determined to be definitively or presumptively without HIV.[16] Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see Initial Postnatal Management of the Neonate Exposed to HIV and *Pneumocystis jirovecii* Pneumonia in the Pediatric Opportunistic Infection Guidelines).

Virologic Testing at Birth for Newborns at High Risk of Perinatal HIV Transmission

Virologic testing at birth should be considered for newborns who are at high risk of perinatal HIV transmission,[17-22] such as infants born to women with HIV who—

- Did not receive prenatal care;
- Received no antepartum ARVs or only intrapartum ARV drugs;
- Initiated ART late in pregnancy (during the late second or third trimester);
- Received a diagnosis of acute HIV infection during pregnancy or in labor; and/or
- Had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received ART and did not have sustained viral suppression.

All infants at high risk of perinatal HIV transmission should have specimens obtained for HIV testing at birth before initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed.

Blood samples from the umbilical cord should not be used for diagnostic evaluation because of the potential for contamination with maternal blood.

Virologic testing at birth is critical for early HIV diagnosis (see When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines). Infants who have a positive virologic test result at or before age 48 hours are considered to have early (intrauterine) infection, whereas non-breastfed infants who have a negative virologic test result during the first week of life and subsequently have positive test results are considered to have late (intrapartum) infection.[17,18,23] Testing at birth also might be considered in instances when there are concerns that a newborn at low risk of perinatal HIV transmission may be lost to follow-up without testing.

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,[15] and early identification of infection permits transition from presumptive HIV therapy to treatment doses of ART (see When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric Antiretroviral Guidelines).

Virologic Testing at Age 1 to 3 Months

Testing performed at age 1 to 3 months is intended to maximize the likelihood of detecting HIV infection in infants. In the HIV Prevention Trials Network 040 study, 93 of 140 infants with HIV (66.4%) were identified at birth. Infants who received negative test results in the first 7 days of life received an HIV diagnosis when the next diagnostic test was performed at 3 months of age.[24] For infants at high risk of perinatal HIV transmission, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission suggests performing an additional virologic test 2 to 6 weeks after ARV drugs are discontinued (i.e., at age 8–12 weeks), given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis or presumptive HIV therapy, may reduce the sensitivity of diagnostic testing.[24,25] In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt diagnosis of HIV in infants with an additional test at 8 to 12 weeks of life (i.e., 2–6 weeks after cessation of prophylaxis or presumptive HIV therapy) to capture additional cases (see Table A below). For infants at low risk of HIV transmission, a single test obtained at 1 to 2 months of age may be timed to occur 2 to 4 weeks after cessation of ARV prophylaxis.

An infant with two negative virologic test results (one at age ≥14 days and the other at age ≥4 weeks), or one negative test result at age ≥8 weeks at least 2 weeks after discontinuing ARV prophylaxis/presumptive therapy, can be viewed as presumptively HIV uninfected, assuming the child has not had a positive prior virologic test result or clinical evidence indicative of HIV infection, and is not breastfed.

Virologic Testing at Age 4 to 6 Months

Infants with HIV exposure who have had negative virologic assays at age 14 to 21 days and at age 1 to 2 months, who have no clinical evidence of HIV infection, and who are not breastfed should be retested at age 4 to 6 months for definitive exclusion of HIV infection.

Table 3. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV According to Risk of Perinatal HIV Acquisition[a]

Infants at High Risk	
Criteria for Infants at High Risk	**Age at HIV NAT Testing for Infants at High Risk**
Infants born to mothers with HIV who— • Did not receive prenatal care; • Received no antepartum ARVs or only intrapartum ARV drugs; • Initiated ART late in pregnancy (during the late second or third trimester); • Received a diagnosis of acute HIV infection during pregnancy or in labor; and/or • Had detectable HIV viral loads (≥50 copies/mL) close to the time of delivery, including those who received ART but did not achieve sustained viral suppression.	Birth[b] 14–21 days 1–2 months 2–3 months[b] 4–6 months All infants at high risk of perinatal HIV transmission should have specimens obtained for HIV testing at birth before initiating an ARV drug regimen; however, presumptive HIV therapy should not be delayed.
Infants at Low Risk	
Criteria for Infants at Low Risk	**Age at HIV NAT Testing for Infants at Low Risk**
Infants born to mothers who— • Received ART during pregnancy; • Had sustained viral suppression (usually defined as <50 copies/mL); *and* • Were adherent to their ARV regimens.	14-21 days 1–2 months[c] 4–6 months

[a] This table summarizes standard time points for HIV virologic diagnostic testing of infants who are not breastfeeding. For information about HIV testing time points for infants born to women with HIV who opt to breastfeed after comprehensive counseling see the Breastfeeding subsection of this chapter below and Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed.

[b] For high-risk infants, virologic diagnostic testing is recommended at birth. For infants treated with multiple ARVs in the first 2 to 4 weeks of life, additional virologic testing is recommended 2 to 6 weeks after ARV drugs are discontinued (i.e., at 8-12 weeks of life).

[c] For low-risk infants, test may be timed to occur at least 2 weeks after cessation of ARV prophylaxis.

Key: ART = antiretroviral therapy; ARV = antiretroviral; NAT = nucleic acid test

Antibody Testing at Age 6 Months and Older

Two or more negative results of HIV antibody tests that were performed in non-breastfed infants at age ≥6 months also can be used to exclude HIV infection definitively in children with no clinical or virologic laboratory-documented evidence of HIV infection.[26,27]

Antibody Testing at Age 18 to 24 Months to Document Seroreversion

In general, no additional HIV testing of any kind (e.g., NAT, antibody, antigen/antibody) is needed routinely for non-breastfed infants who meet the criteria for definitive exclusion of HIV and who have had no known or suspected HIV exposure after birth. However, infants with potential HIV exposure after birth (e.g., breastfeeding, premasticated feeding, sexual abuse, contaminated blood products, percutaneous exposure) who are aged <18 months require additional testing using HIV RNA/DNA NAT assays to establish their HIV status. Infants aged ≥18 months of age who have these potential exposures require HIV antigen/antibody testing.

In a study from 2012, the median age at seroreversion was 13.9 months.[28] Although the majority of infants who do not have HIV will serorevert by age 15 months to 18 months, late seroreversion after 18 months has been reported (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.[28-31]

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion (Aged ≤24 Months)

Non-breastfed children with perinatal HIV exposure, no other HIV transmission risk factor, and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies up to age 24 months. These children are called late seroreverters.[28-31] In one study, 14% of children with HIV exposure did not have HIV seroreverted after age 18 months.[28] More recent data from Thailand associated late seroreversion with the antenatal use of protease inhibitors in pregnant women with HIV. In this study, late seroreversion also was associated with the use of fourth-generation combination antigen/antibody immunoassays.[32] These children may have had positive immunoassay results, but supplemental antibody test results indicated indeterminate HIV status. In such cases, repeat antibody testing at a later date confirmed seroreversion. Due to the possibility of residual HIV antibodies, virologic testing (i.e., with a NAT) is necessary to exclude definitively or confirm HIV infection in children with perinatal HIV exposure who have a positive HIV antibody (or antigen/antibody) test at age 18 months to 24 months. Virologic testing will distinguish late-seroreverting children who do not have HIV but have residual antibodies from children who have antibodies due to underlying HIV infection. Age-appropriate HIV testing also is recommended for infants and children with signs and/or symptoms of HIV, even in the absence of documented or suspected HIV exposure.

Postnatal HIV Infection in Children with Perinatal HIV Exposure and Prior Negative Virologic Test Results for Whom There Are Additional HIV Transmission Risks

In contrast to late seroreverters, in rare situations, postnatal HIV infections have been reported in children with HIV exposure who had prior negative HIV virologic test results. This occurs in children who acquire HIV through an additional risk factor after completion of testing (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months below).

Suspicion of HIV-2 or Non-Subtype B HIV-1 Infections with False-Negative Virologic Test Results

Children with non-subtype B HIV-1 and children with HIV-2 may have false-negative virologic tests but persistent positive immunoassay results.[33-35] The diagnostic approach in these situations is discussed below in Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and in Virologic Assays to Diagnose HIV-2 Infections.

Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months

Breastfeeding

People with HIV should be encouraged to avoid breastfeeding.[36] Monitoring of infants born to people with HIV who opt to breastfeed after comprehensive counseling should include immediate HIV diagnostic virologic testing with a NAT at the following time points: birth, 14 to 21 days, 1 to 2 months, and 4 to 6 months (see Table A above).[37] Many experts then recommend testing every 3 months throughout breastfeeding, followed by monitoring at 4 to 6 weeks, 3 months, and 6 months after cessation of breastfeeding. Clinicians caring for a person with HIV who is considering breastfeeding should consult with an expert and, if necessary, the Perinatal HIV Hotline (1-888-448-8765). For more information, see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection and Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed.

Premastication

Receipt of solid food that has been premasticated or prewarmed (in the mouth) by a caregiver with HIV is associated with risk of HIV transmission.[38-43] If this occurs in children with perinatal HIV exposure aged ≤24 months with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing because they may have residual maternal HIV antibodies (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations above).

Additional Routes of HIV Transmission

Additional routes of HIV transmission in children include sexual abuse, receipt of contaminated blood products, and needlestick with contaminated needles. teIt may be difficult to obtain a history of HIV exposure. Therefore, age-appropriate HIV testing is recommended for infants and children with signs and/or symptoms of HIV infection, even in the absence of documented or suspected perinatal or non-perinatal HIV exposure. Acquisition of HIV in older children is possible through accidental needlestick injuries, sexual transmission, or injection drug use. Medical procedures performed in settings with inadequate infection control practices may pose a potential risk; although tattooing or body piercing presents a potential risk of HIV transmission, no reported cases of HIV transmission from these activities have been documented.[45]

Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with non-perinatal HIV exposure only or in children with perinatal HIV exposure who are aged >24 months relies primarily on HIV antibody and antigen/antibody tests.[1,46] Food and Drug Administration (FDA)–approved diagnostic tests include—

- Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies and HIV-1 p24 antigen. These tests are recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. However, p24 antigen from HIV-1 non-B strains, HIV-1 non-M strains, and HIV-2 strains may not be detected.[47] Recent data suggest that the use of immunoassays and rapid diagnostic test combination algorithms that have limited HIV antigen breadth may not be adequate for diagnosis of HIV infection in children following early treatment with ART.[48]
- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies. This immunoassay is recommended for supplemental testing.
- HIV-1 NAT. A NAT always is indicated as an additional test to diagnose acute HIV infection.

The diagnosis of HIV-2 in children with non-perinatal exposure only or in children with perinatal exposure aged >24 months relies on the 2014 Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories laboratory testing guidelines. These guidelines recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that distinguishes between HIV-1 and HIV-2 antibodies for supplemental testing. When used as a supplemental test, the results of the HIV-1 Western blot are more ambiguous than those of the HIV-1/HIV-2 antibody differentiation immunoassay; >60% of individuals with HIV-2 are misclassified as having HIV-1 by the HIV-1 Western blot.[1,49] All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department; additional HIV-2 DNA PCR testing can be arranged by a local public health laboratory or by CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is inconclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis, although this assay is not commercially available.[50,51]

Virologic Assays to Diagnose HIV in Infants Younger Than 18 Months with Perinatal HIV-1 Exposure

HIV RNA Assays

HIV quantitative RNA assays detect extracellular viral RNA in plasma. Their specificity has been shown to be 100% at birth and at ages 1 month, 3 months, and 6 months and is comparable to the specificity of HIV DNA PCR.[25] Testing at birth will detect HIV RNA in infants who acquire HIV *in utero* and not in those who acquire HIV from exposure during delivery or immediately before delivery (i.e., during the intrapartum period). Studies have shown that HIV RNA assays identify 25% to 58% of infants with HIV infection from birth through the first week of life, 89% at age 1 month, and 90% to 100% by age 2 months to 3 months. These results are similar to the results of HIV DNA PCR for early diagnosis of HIV.[3,25,52]

The sensitivity of HIV RNA assays is affected by maternal antenatal ART or ARV drugs administered to the infant as prophylaxis or presumptive therapy.[53] In one study, the sensitivity of HIV RNA assays was not associated with the type of maternal ART or infant ARV prophylaxis, but HIV RNA levels at 1 month were significantly lower in infants with HIV who were receiving multidrug prophylaxis. In contrast, the median HIV RNA levels were high by age 3 months in both groups after stopping prophylaxis.[25] Between 2010 and 2016, a significant decline in baseline viremia was noted in South Africa's Early Infant Diagnosis program, with loss of detectability documented among some infants with HIV. This decline may have reflected the administration of various prophylactic ARV regimens during those years.[54] Further studies are necessary to evaluate the sensitivity of HIV RNA assays during receipt of multidrug ARV prophylaxis or presumptive HIV therapy in infants whose mothers also received antenatal ART.

An HIV quantitative RNA assay can be used as a confirmatory test for infants who have an initial positive HIV DNA PCR test result. In addition to providing virologic confirmation of infection status, an HIV RNA measurement assesses baseline viral load. An HIV genotype can be performed on the same sample to guide initial ARV treatment in an infant with HIV. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting non-subtype B HIV (see Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections below).

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing. It is the only qualitative RNA test that is approved by the FDA.[23,55-58]

HIV DNA PCR and Related Assays

HIV DNA PCR is a sensitive technique that is used to detect intracellular HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at ages 1 month, 3 months, and 6 months. Studies have shown that HIV DNA PCR assays identify 20% to 55% of infants with HIV infection from birth through the first week of life, with the same caveat as for RNA testing—testing at birth detects only *in utero* HIV infection and not infection in those infants who acquire HIV during the intrapartum period. This percentage increases to >90% by age 2 weeks to 4 weeks and to 100% at ages 3 months and 6 months.[23,25,52]

Two studies provided data on diagnostic testing at different time points in infants with confirmed HIV infection, including those who had negative test results at birth. One study noted that among 47 infants with HIV infection who had negative DNA PCR test results at birth, 68% were identified during the period of neonatal ARV prophylaxis at 4 to 6 weeks; by 3 months, all 47 infants were identified.[24] Another study from Cape Town evaluated the sensitivity of HIV DNA assays within 8 days of life, during and after initiating ART in infants with HIV. The infants had been exposed to a combination of maternal ART *in utero* and ARV drugs for prophylaxis and treatment. In seven infants who achieved virologic suppression (defined as a continuous downward trend in plasma HIV RNA, with <100 copies/mL after 6 months), total HIV DNA continued to decay over 12 months. The authors noted that one infant had undetectable HIV DNA after 6 days on treatment, another had undetectable HIV DNA after 3 months, and a third had undetectable HIV DNA after 4 months, suggesting that rapid decline of HIV-1 RNA and DNA may complicate definitive diagnosis.[59] More recent studies from the same authors suggest that ART initiation within the first week of life reduces persistence of long-lived infected cells and that delaying ART initiation is associated with slower decay of infected cells.[60] A data set of 38,043 infants from the Western Cape province of South Africa who were tested at a median age of 45 days of life showed that infants who received the World Health Organization Option B+ ARV regimen had fewer indeterminate DNA PCR results than infants who were receiving older ARV regimens.[61] Another group of South African investigators reported similar findings in a study of a cohort of 5,743 neonates from Johannesburg who were exposed to HIV.[62]

The AMPLICOR® HIV-1 DNA test has been used widely for diagnosis of HIV in infants born to mothers with HIV-1 infection since it was introduced in 1992. However, it is no longer commercially available in the United States. The sensitivity and specificity of noncommercial HIV-1 DNA tests that use individual laboratory reagents may differ from the sensitivity and specificity of an FDA-approved commercial test. The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 version 2.0 qualitative test (which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots) may be used for HIV diagnosis in infants, but it is not approved by the FDA.[10,11,62] These considerations underscore the importance of testing with HIV NATs at 4 months—well after neonatal ARV prophylaxis or presumptive HIV therapy has stopped.

Other Issues

Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections

Although HIV-1 Group M subtype B is the predominant viral subtype found in the United States, multiple subtypes and recombinant forms also are found in the United States.[63] Data from the CDC National HIV Surveillance System (NHSS) showed that the number of non–U.S.-born children with HIV has exceeded the number of U.S.-born children with HIV since 2011, with 65.5% of non–U.S.-born children with HIV born in sub-Saharan Africa and 14.3% in Eastern Europe.[64] In an evaluation of infants who received a perinatal HIV infection diagnosis in New York State in 2001 and 2002, 16.7% of infants had acquired a non-subtype B strain of HIV, compared with 4.4% of infants born in 1998 and 1999.[65] Among a group of 40 children who visited a pediatric HIV clinic in Rhode Island between 1991 and 2012, 14 (35%) acquired HIV with non-B HIV-1 subtypes. All 14 children were either born outside the United States or their parents were of foreign origin.[66] In an analysis of 1,277 unique sequences collected in Rhode Island from 2004 to 2011, 8.3% were non-B subtypes (including recombinant forms). Twenty-two percent of participants with non-B subtypes formed transmission clusters, including individuals with perinatally acquired infection.[67] In an analysis of 3,895 HIV-1 sequences that were collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms).

Evolving immigration patterns may be contributing to local and regional increases in HIV-1 subtype diversity. Non-subtype B viruses predominate in other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia. Group O HIV strains are seen in West-Central Africa.[68] Non-subtype B and Group O strains may be seen in countries with links to these geographical regions.[69-73] The geographical distribution of HIV groups is available at the HIV Sequence Database.

Real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay are better at detecting non-subtype B HIV infection and the less-common Group O strains than older RNA assays[4-9] (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). An example includes the COBAS®

AmpliPrep/COBAS® TaqMan® HIV-1 qualitative test (a dual-target DNA/RNA test), which also can identify non-subtype B and Group O infections.[10,11]

Thus, a real-time PCR assay, qualitative RNA assay, or a dual-target total DNA/RNA test should be used for infant testing instead of a DNA PCR assay when evaluating an infant born to a mother whose HIV infection is linked to an area that is endemic for non-subtype B HIV or Group O strains, such as Africa or Southeast Asia. Another indication is when initial testing is negative using an HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody test results obtained at age ≥6 months provide further evidence to rule out HIV infection definitively. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or CDC may be able to assist in obtaining referrals for diagnostic HIV testing.

Chimeric Antigen Receptor T-Cell and Lentiviral-Based Gene Therapy May Give Rise to False-Positive HIV NAT Results

Chimeric antigen receptor (CAR) T-cell immunotherapy is a major advancement in cancer therapeutics, including for pediatric B-cell acute lymphoblastic leukemia (B-ALL). Reprogramming of T cells is achieved by using gammaretroviral or lentiviral vectors. Recent reports indicate that these vectors may interfere with long terminal repeat genomes in HIV NAT results and, thus, produce false-positive results. As CAR T-cell therapy becomes more widely available for multiple indications, it will be important for clinicians to recognize that routine HIV-1 NAT results may give rise to false results. In addition, lentiviral vector–based gene therapy as treatment for severe combined immunodeficiency can give rise to false-positive HIV NAT results. Laboratories should, therefore, have appropriate alternate HIV-1 NAT resulting platforms made available for this emerging patient population.[74-78]

Virologic Assays to Diagnose HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Benin, Burkina Faso, Cape Verde, the Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome, Senegal, Sierra Leone, and Togo; and parts of India.[79-81] HIV-2 infection also is well documented in France and Portugal, which have large numbers of immigrants from these regions.[82,83] HIV-1 and HIV-2 coinfection may occur, but this rarely is described outside areas where HIV-2 is endemic. HIV-2 is rare in the United States. Although accurately diagnosing HIV-2 can be difficult, it is clinically important because HIV-2 strains are resistant to several ARV drugs that were developed to suppress HIV-1.[84-86] (See HIV-2 Infection and Pregnancy.)

A mother should be suspected of having HIV-2 if her infection is linked to an area that is endemic for HIV-2 infection or if her HIV test results are suggestive of HIV-2 infection (i.e., the mother has a positive initial HIV 1/2 immunoassay test result and HIV-1 RNA viral loads that are at or below the limit of detection). The current recommendation is to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing.[1] Between 2010 and 2017, an increase in the number of HIV-1/HIV-2 differentiation test results was reported to the CDC's NHSS. More than 99.9% of all HIV infections identified in the United States were categorized as HIV-1, and the number of HIV-2 diagnoses (mono-infection or dual-infection) remained extremely low (<0.03% of all HIV infections).[87]

Infant testing with HIV-2–specific DNA PCR tests should be performed at time points similar to those used for HIV-1 testing when evaluating an infant born to a mother with known or suspected HIV-2 infection. HIV-2 DNA PCR testing can be arranged by the HIV surveillance program of the state or local health department through their public health laboratory, or the CDC, because this assay is not commercially available.[50,51] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[79,88]

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Clinical and Laboratory Monitoring of Pediatric HIV Infection

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• Absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of HIV diagnosis and, if a child is not started on antiretroviral therapy (ART) after diagnosis, this monitoring should be repeated at least every 3 to 4 months thereafter **(AIII).**
• Absolute CD4 count is recommended for monitoring immune status in children with HIV of all ages, with CD4 percentage as an alternative for children aged <5 years **(AII).**
• Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy in all ART-naive patients, and before switching regimens in patients with treatment failure **(AII).** Genotypic resistance testing is preferred for this purpose **(AIII).**
• After initiation of ART or after a change in ARV regimen, children should be evaluated for clinical adverse effects and should receive support for treatment adherence within 1 week to 2 weeks; laboratory testing for toxicity and viral load response is recommended at 2 to 4 weeks after treatment initiation or change in ARV regimen **(AIII).**
• Children on ART should be monitored for therapy adherence, effectiveness, and toxicities routinely (every 3–4 months) **(AII*).** See the sections on Adherence to Antiretroviral Therapy in Children and Adolescents with HIV and Management of Medication Toxicity or Intolerance.
• Additional CD4 count and plasma viral load monitoring should be performed to evaluate children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value **(AIII).** CD4 count can be monitored less frequently (every 6–12 months) in children and adolescents who are adherent to therapy, who have sustained virologic suppression and CD4 count values that are well above the threshold for opportunistic infection risk, and who have stable clinical status **(AII).** Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence **(AIII).**
• Phenotypic resistance testing should be considered (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after a patient has experienced virologic failure on multiple ARV regimens **(CIII).**
• Review the history of all previously used ARVs and available resistance test results when making decisions about choice of new ARVs, because mutations may not be detected once the prior drugs have been discontinued **(AII).**
• Viral co-receptor tropism assays are recommended whenever a CCR5 antagonist is being considered for treatment **(AI*).** The use of tropism assays also should be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist **(AI*).**

__Rating of Recommendations:__ A = Strong; B = Moderate; C = Optional

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

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

Laboratory monitoring of children living with HIV poses unique and challenging issues. In particular, the normal ranges of CD4 T lymphocyte (CD4) counts and plasma HIV RNA concentrations (viral loads) can vary significantly by age. The CD4 counts and viral load values that predict the risk of disease progression also change as a child ages. This section will address immunologic, virologic, general laboratory, and clinical monitoring of children with HIV, with information that is relevant to both those who have recently received an HIV diagnosis and those who are receiving antiretroviral therapy (ART).

Clinical and Laboratory Monitoring of Children with HIV

Initial Evaluation of Children Who Recently Received an HIV Diagnosis, or Entering or Transferring to a New Care Setting

Children who have recently received an HIV diagnosis should have their CD4 counts and plasma viral loads measured, their growth and development should be evaluated for signs of HIV-associated abnormalities, and a complete physical examination should be performed to identify physical findings of HIV disease (e.g., lymphadenopathy, hepatosplenomegaly, hyperreflexia, ankle clonus). Testing also should be performed to assess for HIV-associated conditions, including anemia, leukopenia, thrombocytopenia, hypoalbuminemia, nephropathy (urinalysis), hyperglycemia, hepatic transaminitis, and renal insufficiency (creatinine). In addition, children with HIV should have a complete, age-appropriate medical history and physical examination (see Table 5 below). Opportunistic infection (OI) monitoring should follow the guidelines that are appropriate for the child's exposure history and clinical setting (see the Pediatric Opportunistic Infection Guidelines). Children with HIV who are relocating from outside the United States may benefit from additional evaluations—such as screening for tuberculosis, gastrointestinal parasites, hepatitis infection, lead level—and thyroid function studies.

Laboratory confirmation of HIV infection should be obtained when available documentation is incomplete (see Diagnosis of HIV Infection in Infants and Children). Genotypic resistance testing should be performed, even if ART is not initiated immediately. In addition, a full antiretroviral (ARV) drug history should be obtained; this history should include any exposure to ARV drugs for the prevention of perinatal HIV transmission (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). If abacavir (ABC) is being considered as a component of the regimen, HLA-B*5701 testing should be conducted prior to initiating ABC, and an alternative ARV drug should be used if the HLA-B*5701 test result is positive[1] (see the Abacavir section in Appendix A: Pediatric Antiretroviral Drug Information).

Before initiating therapy or making changes to a patient's ARV regimen, a clinician and multidisciplinary team members (where available) should assess potential barriers to adherence and discuss the importance of adherence with the patient and/or their caregiver (see Adherence to Antiretroviral Therapy in Children and Adolescents with HIV).

If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 count and plasma viral load should be monitored at least every 3 to 4 months.

Evaluation at Initiation of Antiretroviral Therapy

At the time of ART initiation, a physical examination should be performed, including assessment of weight and height, and baseline labs for CD4 count and plasma viral load should be obtained to monitor ART response (see Table 5 below). To set the baseline for monitoring ART toxicity (see Management of Medication Toxicity or Intolerance), a complete blood count, urinalysis, and serum chemistry panel (including levels of electrolytes, creatinine, glucose, and hepatic transaminases) should be performed (see Table 5 below). The levels of serum lipids (cholesterol and triglycerides) also should be measured. For information about the adverse effects (AEs) associated with a specific ARV drug, see Tables 15a–15k in Management of Medication Toxicity or Intolerance and Appendix A: Pediatric Antiretroviral Drug Information for complete information on each drug.

Clinical and Laboratory Monitoring After Initiating or Changing an Antiretroviral Regimen

Children who start ART or who change to a new regimen should be monitored to assess the effectiveness, tolerability, and AEs of the regimen and to evaluate medication adherence. Clinicians and multidisciplinary teams should schedule frequent clinical in-person and/or telemedicine visits to monitor patients closely during the first few months after initiating a new ARV regimen. Telemedicine visits and telehealth communication platforms are particularly relevant to the care of adolescent patients based on their technology access and habits.[2] Additional check-ins via telephone and/or telehealth (emails, text messaging, app-based communications) may support adherence and early identification of medication side effects. The continuity of patient and caregiver interactions is an opportunity for clinicians and the multidisciplinary team to provide support and discuss adherence with patients and their caregivers.

A recent systematic review of randomized controlled trials from the last 10 years that used a telemedicine approach as a study intervention or assessed telemedicine as a subspecialty of pediatric care found that telemedicine services for the general public and pediatric care are comparable to or better than in-person services.[3] Use of telemedicine as a remote, technology-based access to clinical services in HIV care is growing and has been shown to achieve similar outcomes as those associated with in-person care. People with HIV on ART achieve similar clinical responses to therapy, adherence to treatment, quality-of-life scores, and psychological and emotional status, whether treated through telemedicine or in person.[4-6] When selecting the format for clinical follow-up, it is important to recognize differences and similarities between in-person and telemedicine visits (see Table 4 below). The benefits of telemedicine visits include patient and caregiver convenience, lack of travel, flexibility, and ability to visualize ART handling/swallowing and conduct directly observed therapy in the home setting. Telemedicine visits, however, require technological access/capacity and limit the provider's ability to conduct physical examinations and obtain laboratory testing on site.[4,5] Periodic measurements of body weight, which are important for dose modification in rapidly growing infants and to monitor for excessive weight gain as a possible AE of some ARVs, are not possible with telemedicine visits. Additionally, providers need to arrange and coordinate access to the laboratory testing and be familiar with state and local requirements for carrying out, documenting, and billing telemedicine visits. Although both in-person and telemedicine visits involve considerations for stigma, privacy, and confidentiality, these considerations differ between health care and home/community-based settings. For example, the caregiver who has not disclosed the HIV and ART status of the child at home might prefer in-person visits at the clinic or specific hours and/or alternative locations for a telemedicine visit.

Table 4. Characteristics and Requirements for In-Person Clinic Visits vs. Telemedicine Visits

	In-Person Visits	Telemedicine Visits
Patient/caregiver convenience		✓
Flexibility (time and locations) of appointments		✓
Confidentiality concerns	✓	✓
Directly observed therapy in home settings		✓
Physical assessment (e.g., skin rashes)	✓	✓
Physical exam, including weight and height	✓	
Adherence support and counseling	✓	✓
Mental health assessment and counseling	✓	✓
Multidisciplinary support (assessment and coordination of nutritional and social services)	✓	✓
Laboratory testing on site	✓	
Travel to clinic	✓	
Technology requirements (internet access, equipment, skills)		✓
Legal and administrative guidelines for visit documentation and billing	✓	✓

The first few weeks of ART can be particularly difficult for children and their caregivers; they must adjust their schedules to allow consistent and routine administration of medication doses. Children also may experience the AEs of medications, and both children and their caregivers need assistance to determine whether the effects are temporary and tolerable or whether they are more serious or long term and require a clinical visit. It is critical that providers communicate with caregivers and children in a supportive, nonjudgmental manner and use plain language. This approach promotes interactive reporting and ensures that providers can have a productive dialogue with both children and their caregivers, particularly in situations where medication adherence is reported to be inconsistent.

Within 1 Week to 2 Weeks of Initiating Antiretroviral Therapy

Within 1 week to 2 weeks of initiating ARV therapy, children should be evaluated either in person, through telemedicine, or by telephone. During this evaluation, clinicians should identify clinical AEs and provide support for adherence. Many clinicians plan additional contacts (in person, through telemedicine, by telephone, or via email/texts/apps) with children and caregivers to support adherence during the first few weeks of therapy.

2 to 4 Weeks After Initiating Antiretroviral Therapy

Most experts recommend performing laboratory testing at 2 to 4 weeks (but no later than 8 weeks) after initiating ART to assess virologic response and laboratory toxicity, although this recommendation is based on limited data. The laboratory chemistry tests that a patient requires will depend on the ARV regimen that the patient is receiving (see Table 5 below). Plasma viral load monitoring is important as a marker of response to ART, because a decline in viral load suggests that the patient is adherent to the regimen, that the appropriate doses are being administered, and that the virus is susceptible to the drugs in the regimen. Some experts favor measuring viral load at 2 weeks to ensure that viral load is declining. A significant decrease in viral load should be observed 4 to 8 weeks after initiation of ART.

Clinical and Laboratory Monitoring for Children Who Are Stable on Long-Term Antiretroviral Therapy

After the initial phase of ART initiation (1–3 months), clinicians should assess a patient's adherence to the regimen and the regimen's effectiveness (as measured by CD4 count and plasma viral load) every 3 to 4 months. Additionally, clinicians should review a patient's history of drug toxicities and evaluate each patient for any new AEs using physical examinations and the relevant laboratory tests. If laboratory evidence of toxicity is identified, testing should be performed more frequently until the toxicity resolves.

Table 5 below provides one proposed general monitoring schedule, which should be adjusted based on the specific ARV regimen that a child is receiving.

A patient's baseline CD4 count affects how rapidly CD4 count improves after ART initiation; children with very low CD4 counts may take longer than 1 year to achieve their highest values after viral load suppression.[7]

Studies that have critically evaluated the frequency of laboratory monitoring in both adults and children, particularly CD4 count and plasma viral load, support less frequent monitoring in stable patients who have been consistently virologically suppressed for ≥1 year.[8-14]

The Adult and Adolescent Antiretroviral Guidelines currently support performing plasma viral load testing every 6 months for individuals who have both—

- Consistent virologic suppression ≥2 years; *and*
- CD4 counts that are consistently >300 cells/mm^3.

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV finds value in continuing to perform viral load testing every 3 to 4 months to provide enhanced monitoring of adherence or disease progression among children and adolescents. Some experts monitor CD4 count less frequently (e.g., every 6–12 months) in children and adolescents who are adherent to therapy, who have CD4 count values well above the threshold for OI risk, and who have had sustained virologic suppression and stable clinical status for >2 to 3 years.[15] Some clinicians find value in scheduling visits every 3 months, even when laboratory testing is not performed, in order to review adherence and update drug doses for interim growth. Follow-up clinical and laboratory monitoring can be conducted through in-person and/or telemedicine visits. Additional arrangements, coordination, and follow-up of the laboratory testing (e.g., using local laboratory or primary care provider's office) may be required for telemedicine visits.

Testing at the Time of Switching Antiretroviral Regimens

When a patient switches regimens to simplify ART, clinicians should obtain the appropriate laboratory test results at baseline for the toxicity profile of the new regimen. Follow-up should include a measurement of plasma viral load at 4 weeks (and not >8 weeks) after the switch to ensure that the new regimen is effective. If the regimen is switched because the regimen is failing (see Recognizing and Managing Antiretroviral Treatment Failure), resistance testing should be performed while a patient is still receiving the failing regimen. This optimizes the chance of identifying resistance mutations, because resistant strains may revert to wild type within a few weeks of stopping ARV drugs (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Clinicians should consider performing phenotypic resistance testing, including co-receptor tropism testing, in addition to genotypic viral resistance testing in children who have experienced prolonged or repeated periods of viral nonsuppression on multiple ARV regimens.[16]

Immunologic Monitoring in Children: General Considerations

When interpreting CD4 counts and percentages in children, clinicians must consider age as a factor. CD4 count and percentage values in healthy infants without HIV are considerably higher than values observed in adults without HIV; these infant values slowly decline to adult values by age 5 years. An analysis from the HIV Paediatric Prognostic Markers (HPPM) Collaborative Study found that CD4 percentage provided little or no additional prognostic value compared with CD4 count regarding short-term disease progression in children aged <5 years; similar results were reported in a study of older children.[17] The current pediatric HIV disease classification is based on absolute CD4 count, which is the preferred assay for monitoring and estimating the risk for disease progression and OIs[18] (see Table A. HIV Infection Stage Based on Age-Specific CD4 Count or Percentage in Appendix C: CDC Pediatric HIV CD4 Cell Count/Percentage and HIV-Related Diseases Categorization).

In children with HIV, as in adults with HIV, CD4 count and percentage decline as HIV infection progresses; patients with lower CD4 counts or percentage values have a poorer prognosis than patients with higher values (see Tables A–C in Appendix D: Supplemental Information).

Medical practice guidelines now recommend that all people with HIV receive ART, regardless of their CD4 count and clinical stage. However, CD4 counts are used to determine risk profiles that affect the urgency of recommendations for when to initiate therapy in an ART-naive child with HIV infection and when to initiate OI prophylaxis (see When to Initiate Therapy in Antiretroviral-Naive Children). A meta-analysis from the HPPM Collaborative Study generated plots that can be used to estimate the short-term risk of progression to AIDS or death in the absence of effective ART, according to age and the most recent CD4 percentage/absolute CD4 count or HIV RNA viral load measurement.[19]

CD4 counts and percentages can show considerable intrapatient variation.[20] Mild intercurrent illness, the receipt of vaccinations, or exercise can produce a transient decrease in CD4 count and percentage; thus, CD4 count and percentage are best measured when patients are clinically stable. Clinical decisions, especially those regarding therapy changes, should be made in response to confirmed changes in CD4 count or percentage in conjunction with a confirmed viral load determination. The CD4 count or percentage and viral load measurement should be confirmed by performing these tests a second time, at least 1 week after the first tests.

HIV RNA Monitoring in Children: General Considerations

Quantitative HIV RNA assays measure the plasma concentration of HIV RNA as copies/mL. Without therapy, plasma viral load initially rises to peak level during the period of primary infection in adults and adolescents, and then declines by as much as 2 to 3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6 to 12 months after acute infection.[21,22] In adults with HIV, the virologic set point correlates with the subsequent risk of disease progression or death in the absence of therapy.[23]

The pattern of change in plasma viral load in untreated infants with perinatal HIV differs from that in adults and adolescents with HIV. High plasma viral loads persist in untreated children for prolonged periods.[24,25] In one prospective study of infants with perinatal infection who were born prior to ARV drug availability for children, plasma viral loads generally were low at birth (i.e., <10,000 copies/mL), increased to high values by age 2 months (most infants had values >100,000 copies/mL, ranging from undetectable to nearly 10 million copies/mL), and then decreased slowly with a mean plasma viral load of 185,000 copies/mL during the first year of life.[26] After the first year of life, plasma viral load slowly declined during the next few years.[26-29] Viral load during the first 12 to 24 months after birth showed an average decline of approximately 0.6 $\log_{10}$ copies/mL per year, followed by an average decline of 0.3 $\log_{10}$ copies/mL per year until age 4 to 5 years. This pattern probably reflects the lower efficiency of a developing immune system in containing viral replication and, possibly, the rapid expansion of HIV-susceptible cells that occurs with somatic growth.[30]

Despite the established association between high plasma viral load and disease progression, a specific HIV RNA concentration has only moderate predictive value for disease progression and death in an individual child.[28] Plasma viral load may be difficult to interpret during the first year of life, because values are high and are less predictive of disease progression risk than those in older children.[25] In both children and adults with HIV, CD4 count or percentage and plasma viral load are independent predictors of disease progression and mortality risk, and using the two markers together more accurately define prognosis.[28,29,31,32]

Methodological Considerations When Interpreting and Comparing HIV RNA Assays

Based on accumulated experience with currently available assays, the current definition of virologic suppression is a plasma viral load that is below the quantification limit of the assay used (generally <20 copies/mL to 75 copies/mL). This definition of suppression has been much more thoroughly investigated in adults with HIV than in children with HIV (see the Adult and Adolescent Antiretroviral Guidelines). Temporary viral load elevations ("blips") that are between the level of detection and 200 copies/mL to 500 copies/mL are often detected in adults[33] and children who are on ART[34]; these temporary elevations do not represent virologic failure as long as the values have returned to below the level of detection when testing is repeated. For definitions and management of virologic treatment failure, see Recognizing and Managing Antiretroviral Treatment Failure. These definitions of virologic suppression and virologic failure are recommended for clinical use. Research protocols or surveillance programs may use different definitions.

Several different methods can be used for quantitating HIV RNA, each of which has a different level of sensitivity (see Table 6 below). Although the results of the assays are correlated, the absolute HIV RNA copy number obtained from a single specimen tested by two different assays can differ by 0.3 $\log_{10}$ copies/mL (a twofold difference) or more.[35-37] Because different assays use different methods to measure HIV RNA, and because the tests have different levels of sensitivity, clinicians should consistently use a single HIV RNA assay method to monitor an individual patient when possible.[38-40]

The predominant HIV-1 subtype in the United States is subtype B, and early assays were designed to detect this subtype. Current kit configurations for all companies have been designed to detect and quantitate essentially all viral subtypes (see Diagnosis of HIV Infection in Infants and Children). This ability is important in many regions of the world where non-B subtypes are predominant, as well as in the United States where a small subset of individuals contract non-B viral subtypes.[38,41-45] It is particularly relevant for immigrant and adopted children who are born outside the United States or to non–U.S.-born parents.

Biologic variation in plasma viral load within one person is well documented. In adults, repeated measurements of plasma viral load using the same assay can produce results that vary by as much as 0.5 $\log_{10}$ copies/mL (a threefold difference) in either direction during the course of a day or on different days.[31,36] This biologic variation may be greater in infants and young children with HIV. This inherent biologic variability must be considered when interpreting changes in plasma viral load in children. Thus, after repeated testing, only differences >0.7 $\log_{10}$ copies/mL (a fivefold difference) in infants aged <2 years and differences >0.5 $\log_{10}$ copies/mL (a threefold difference) in children aged ≥2 years should be considered reflective of plasma viral load changes that are biologically and clinically significant.

Generally, no change in ARV treatment should be made as a result of a change in plasma viral load, unless the change is confirmed by a second measurement. Because of the complexities of HIV RNA testing and the age-related changes in plasma viral load in children, clinicians should consult an expert in pediatric HIV infection when making clinical decisions based on plasma viral loads.

Genetic Testing for Management of HIV

Modern disease intervention strategies often employ genetic testing to evaluate the genes of humans and pathogens. This approach to treatment is an important component in the rise of precision medicine. Clinicians who manage HIV have routinely probed HIV genetic sequences for mutations that are associated with HIV drug resistance. Some ARV drugs are metabolized differently based on specific human genotypes. For example, studies have shown that certain genotypes can affect efavirenz exposure in young children.[46,47] In addition, some human genetic polymorphisms are associated with drug toxicity or AEs (e.g., using HLA-B*5701 testing to predict ABC hypersensitivity)[48]; for more information, see the Abacavir section in Appendix A: Pediatric Antiretroviral Drug Information. Future clinical practice will likely feature broader applications of multiple forms of genetic testing to guide management of health and disease.

Table 5. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy[a]

Laboratory Testing	Entry Into Care[a]	Pre-Therapy[b]	ART Initiation[c]	Weeks 1–2 on Therapy	Weeks 2–4 on Therapy	Every 3–4 Months[d]	Every 6–12 Months[e]	Virologic Failure (Prior to Switching ARV Regimens)
Medical History and Physical Examination[f,g]	✓	✓	✓	✓	✓	✓		✓
Adherence Evaluation[g]		✓	✓	✓	✓	✓		✓
CD4 Count	✓	✓	✓			✓		✓
Plasma Viral Load	✓	✓	✓		✓	✓		✓
Resistance Testing	✓							✓
CBC with Differential[d]	✓	✓	✓		✓	✓		✓

Chemistries[d,h]	✓	✓	✓		✓	✓		✓
Lipid Panel[e]	✓		✓				✓	
Random Plasma Glucose[i]			✓				✓	
Urinalysis	✓		✓				✓	
HBV Screening[j]		✓						✓
Pregnancy Test for Girls and Young Women of Childbearing Potential[k]	✓	✓	✓					✓

[a] See the texts on immunologic, virologic, general laboratory, and clinical monitoring of children with HIV for details on recommended laboratory tests to perform.

[b] When abacavir (ABC) is being considered as part of the regimen, conduct HLA-B*5701 testing prior to initiating ABC and choose an alternative ARV drug if the patient is HLA-B*5701 positive (see the Abacavir section in Appendix A: Pediatric Antiretroviral Drug Information). Genotype resistance testing is recommended if it has not already been performed (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Send tests that are appropriate for the toxicity profile, which is associated with the patient's ARV regimen and the patient's medical history.

[c] If ART is initiated within 30 to 90 days of a pre-therapy laboratory result, repeat testing may not be necessary.

[d] CD4 count, CBC, and chemistries can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy, who have CD4 count values that are well above the threshold for opportunistic infection risk, and who have had sustained virologic suppression and stable clinical status for more than 2 to 3 years. Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.

[e] If lipid levels have been abnormal in the past, more frequent monitoring may be needed. For patients treated with TDF, more frequent urinalysis should be considered.

[f] Pay special attention to changes in weight that might occur after altering an ARV regimen. Weight gain or weight loss may occur when using some ARV drugs (see Table 15h. Lipodystrophies and Weight Gain).

[g] Virtual visits may be appropriate at some time points, particularly for adherence assessments and for visits for established patients, see Table 4 above.

[h] Chemistries refer to a comprehensive metabolic panel. Some experts perform a comprehensive panel at entry and routinely test Cr, ALT, AST and with additional tests tailored to the history of the individual patient.

[i] Random plasma glucose is collected in a gray-top blood collection tube or other designated tube. Some experts would consider monitoring HgbA1C in children at risk for prediabetes/diabetes rather than routine blood glucose.

[j] This screening is only recommended for individuals who have previously demonstrated no immunity to HBV and who are initiating a regimen that contains ARV drugs with activity against HBV, specifically 3TC, FTC, TAF, or TDF.

[k] See the Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV in the Perinatal Guidelines.

Key: 3TC = lamivudine; ABC = abacavir; ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; CBC = complete blood count; CD4 = CD4 T lymphocyte; Cr = creatinine; FTC = emtricitabine; HBV = hepatitis B virus; HgbA1C = glycosylated hemoglobin; OI = opportunistic infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Table 6. Primary Food and Drug Administration-Approved Assays for Monitoring Viral Load

Assay	Abbott Real Time	NucliSens EasyQ v2.0	COBAS AmpliPrep/ TaqMan v2.0	Versant v1.0	Aptima HIV-1 Quant Assay
Method	Real-time RT-PCR	Real-time NASBA	Real-time RT-PCR	Real-time RT-PCR	Real-time TMA
Dynamic Range	40–10^7 copies/mL	25–10^7 copies/mL	20–10^7 copies/mL	37–11×10^7 copies/mL	30–10^7 copies/mL
Specimen Volume[a]	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL	≥0.4 mL
Manufacturer	Abbott Laboratories	bioMerieux	Roche	Siemens	Hologic, Inc.

[a] Laboratories often request large blood volumes for standard viral load testing. Consider contacting the local laboratory to determine minimum blood volume required to run the assay. Smaller volumes for children can be accommodated.

Key: NASBA = nucleic acid sequence-based amplification; RT-PCR = reverse transcription-polymerase chain reaction; TMA = transcription-mediated amplification

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When to Initiate Therapy in Antiretroviral-Naive Children

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection (**AI** for children aged <3 months, **AI*** for older children).   ○ Rapid ART initiation (defined as initiating ART immediately or within days of HIV diagnosis), accompanied by a discussion of the importance of adherence and provision of subsequent adherence support, is recommended for all children with HIV. • If a child with HIV has not initiated ART, health care providers should closely monitor the virologic, immunologic, and clinical status at least every 3 to 4 months **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *†Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Overview

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends initiating treatment for all children with HIV. Multiple studies have shown a benefit to early antiretroviral therapy (ART) initiation,[1-3] and that ART initiation within the first year of life is associated with reduced size of viral reservoirs.[4-8] Ongoing viral replication may be associated with persistent inflammation and the development of cardiovascular, kidney, and liver disease and malignancy; studies in adults suggest that early control of viral replication may reduce the risk of these non-AIDS complications.[9-13]

In addition to the health benefits of rapid treatment initiation, which is defined as therapy that is initiated immediately or within days of HIV diagnosis, treatment initiation in young infants with HIV during the early stages of infection may control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species.[14] Initiation of therapy at higher CD4 counts has been associated with the presence of fewer drug-resistant mutations at virologic failure in adults.[15] Early therapy also preserves immune function and prevents clinical disease progression.[16-18]

Survival and Health Benefits Associated with Early Initiation of ART

The Children with HIV Early Antiretroviral Therapy (CHER) trial was a randomized clinical trial in South Africa that initiated triple-drug ART in asymptomatic infants aged 6 to 12 weeks with perinatally acquired HIV and normal CD4 percentages (>25%). Immediate initiation of ART resulted in a 75% reduction in early mortality among these infants, compared with delaying treatment until the infants met clinical or immune criteria.[2] Consistent with the CHER trial, data from a number of observational studies in the United States, Europe, and South Africa demonstrated that infants who received early treatment were less likely to progress to AIDS or death, and they also had improved growth compared with those who started treatment later.[19-22]

In general, studies that evaluate later initiation of ART in children have a selection bias, because children with perinatal infection and rapidly progressing disease may have died prior to receiving an HIV diagnosis or ART, and children who present later for ART initiation may be slower progressors with a better prognosis. However, a general trend toward lower mortality and better growth with earlier ART initiation was reported in an evaluation of observational data from 20,756 ART-naive children aged 1 year to 16 years at enrollment from 19 cohorts in Europe, Southern Africa, and West Africa.[1] Children aged <10 years at enrollment had lower mortality and higher mean height-for-age z score after 5 years of follow-up among participants who initiated ART immediately than those who delayed treatment until their CD4 counts decreased to <350 cells/mm^3. The multicenter, open-label Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) trial randomized 300 children with HIV aged 1 year to 12 years at enrollment (median age 6.4 years) to immediately initiate ART or to defer treatment until their CD4 percentage was <15%; the study reported better height gain among children who started ART immediately.[23] Similarly, other studies have reported an association between younger age at initiation of ART and more rapid growth reconstitution.[20,24-26] Studies conducted in and outside the United States have reported an association between delayed ART initiation and delay of pubertal development and menarche.[27-29] In a study of Zimbabwean children (median age 11 years), earlier ART initiation and improved nutrition were positively associated with improved lung function.[30] Finally, among 32 youths with perinatally acquired HIV from the Pediatric HIV/AIDS Cohort Study (PHACS), DNA methylation evaluating epigenetic aging was compared to chronologic aging over time. Higher viral load and lower CD4 count were associated with epigenetic aging that exceeded chronologic aging, highlighting the value of achieving early viral suppression and maintaining or reconstituting immune function as close to an HIV diagnosis as possible.[31]

Neurodevelopmental Benefits Associated with Early Initiation of ART

A CHER trial substudy found that infants who initiated ART early had significantly better gross motor and neurodevelopmental profiles than those whose therapy was deferred.[32] In a cohort from Thailand, the prevalence of global developmental impairment was 22% (95% confidence interval [CI], 11% to 27%) among children with HIV who initiated ART within 3 months of birth, compared with 44% (95% CI, 23% to 66%) among children who initiated ART from 3 to 12 months.[33] A study of South African infants with perinatal HIV infection who initiated ART within 21 days of life (median 6 days) found that neurodevelopmental scores at 11 months of age for these infants were within the normal range.[34]

Immune Benefits Associated with Early Initiation of ART

In the CHER study, infants who were treated early had decreased immune activation, greater recovery of CD4 cells, expanded CD4-naive T cells, and retention of innate effector frequencies, resulting in greater immune reconstitution than that achieved in infants who received deferred ART.[18] In a small study in Botswana, infants who initiated ART within the first 7 days of life were found to have decreased immune activation, a more polyfunctional HIV-1-specific CD8 cell response, and a markedly reduced HIV latent reservoir, compared with infants who initiated ART later in the first year of life.[7] Among two cohorts of South African infants with HIV, those who initiated ART at ages <6 months had better sustained viral control after achieving suppression than infants who started ART between 6 and 24 months.[3] Available data suggest that both children and adults who initiate treatment with a higher CD4 percentage or CD4 count have better immune recovery than patients who initiate treatment with lower CD4 percentages or CD4 counts.[25,35-37] Among 1,236 children with perinatally acquired HIV in the United States, only 36% of those who started ART with CD4 percentages <15% achieved CD4 percentages >25% after 5 years of therapy, compared with 59% of children who started with CD4 percentages of 15% to 24%.[38] Finally, earlier age at ART initiation results in higher rates of CD4:CD8 ratio normalization and improved immunogenicity of childhood vaccines.[39-41]

Early initiation of suppressive ART (i.e., in infants aged <6 months) results in a significant proportion of infants with HIV who fail to produce their own HIV-specific antibodies. These infants appear to be HIV-seronegative when tested; however, viral reservoirs remain, and viral rebound occurs if ART is stopped.[42-46]

Viral Suppression and Viral Reservoirs with Early Initiation of ART

Early initiation of ART within the first 7 days of life, compared with initiation between 8 and 28 days of life, resulted in a fourfold faster time to viral suppression among infants in a multinational study.[47] Similarly, in a European and Thai cohort of infants with perinatal HIV acquisition and treatment initiation <6 months of age, multivariable analysis showed that younger age at ART initiation (adjusted hazard ratio: 0.84 [95% CI, 0.78–0.91] per month older) was found to be a predictor of faster virological suppression.[48] Other studies have reported that early treatment of infants with perinatally acquired HIV is also associated with reduced size of viral reservoirs.[49] For example, several studies that compared the size of viral reservoirs in children who initiated ART before age 12 weeks with those in children who initiated ART at ≥12 weeks to ≤2 years of age found that viral reservoir size (as measured by peripheral blood mononuclear cell [PBMC] HIV DNA levels) after 1 year and 4 years of ART significantly correlated with the age at ART initiation and the age at viral control.[50-52] Among children in the Early-treated Perinatally HIV-infected individuals: Improving Children's Actual Life with Novel Immunotherapeutic Strategies (EPIICAL) Consortium who initiated ART at a median of 2.3 (interquartile range [IQR] 1.2–4.1) months of age, earlier initiation was associated with lower viral reservoir size, with a 1-month delay in ART initiation associated with a 13% increase in HIV-1 DNA.[5] In addition, 27 children (also in the EPIICAL cohort) who initiated ART before 2 years of age and maintained a viral load <50 copies/mL for more than 5 years had reduced total HIV-1 DNA levels measured at a median of 12 years after treatment initiation (IQR 7.3–15.4), with younger age and viral load at the time of ART initiation each associated with lower reservoir levels.[53] Finally, among 11 infants in the CHER trial who initiated ART between 2.0 and 11.1 months of age and maintained sustained viral suppression, proviral amplification and sequencing of DNA from PBMCs obtained 6 and 9 years after treatment initiation detected only seven (1%) proviral replication competent sequences among three children who initiated treatment after 2.3 months of age, whereas no replication competent proviral sequences were detected in four children who initiated treatment prior to 2.3 months of age.[54] A study of 145 early-treated infants from South Africa[4] found that the risk of viral rebound to >50 copies/mL was twofold higher ($P = 0.0006$) in the first 36 months after treatment initiation for infants with baseline HIV DNA reservoir levels >55 copies/10^6 cells than for infants with HIV DNA reservoir levels ≤55 copies/10^6 cells.

These findings may indicate that initiating ART soon after an infant acquires HIV can limit the size of the HIV viral reservoir, and that smaller reservoirs provide some level of protection against viral rebound in the setting of treatment nonadherence—a frequent event for infants with HIV who are destined for lifelong treatment. Furthermore, near-complete control of viral replication has been reported in infants who initiated ART early and who had sustained control of plasma viremia.[42,55]

The report of a prolonged remission in a child with perinatally acquired HIV in Mississippi generated discussion about early initiation of ART as presumptive treatment in newborns at high risk of HIV acquisition. This newborn, born to an ART-naive mother, was treated with a three-drug antiretroviral (ARV) regimen at age 30 hours, which was continued following diagnostic testing that confirmed HIV infection. ART was given through age 18 months when the parent discontinued the child's treatment. Intensive follow-up virologic evaluations were negative until 27 months after ART discontinuation—when the plasma viral load rebounded to 16,750 copies/mL—confirmed with repeat testing. ART was restarted with rapid achievement of viral suppression.[56,57] A second child from the CHER study with HIV-1 viral load of >750,000 copies/mL at 39 days of life was randomized to ART initiation at 61 days of age for 40 weeks. As of 2019, at the age of 9.5 years, the child remains off ART and HIV-1 is detectable only at very low levels (plasma RNA 6.6 copies/mL), and no replication competent virus is detectable.[58]

These experiences have prompted increasing support for initiating treatment as soon as the diagnosis is made, and if possible, during the first weeks of life to limit reservoir formation and possibly facilitate ART-free remission. Although a limited number of case reports describe lengthy remissions in children with perinatally acquired HIV who have undergone treatment interruption, current ARV regimens have not been shown to eradicate HIV infection, because HIV persists in CD4 cells and other long-lived cells.[58-61] For these reasons, the Panel **does not recommend** empiric treatment interruption outside of a clinical trial setting.

Managing treatment in neonates with HIV is complex from a medical and social perspective. Because of limited safety and pharmacokinetic (PK) data for ARV drugs in full-term infants aged <2 weeks and preterm infants aged ≤4 weeks, drug and dose selection in this age group is challenging[62,63] (see What to Start and Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). Hepatic and renal function are immature in newborns who are undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children.[64,65] When drug concentrations are subtherapeutic—either because of inadequate dosing, poor absorption, or incomplete adherence—ARV drug resistance can develop rapidly, particularly in young infants who experience high levels of viral replication. Frequent follow-up for dose optimization during periods of rapid growth is especially important when treating young infants. Furthermore, clinicians should continually assess a patient's adherence and address potential barriers to adherence during this time (see Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV).

Summary

Multiple studies have reported that early ART initiation is associated with immune, growth, and neurodevelopmental benefits. In addition, early ART initiation may limit the formation of the viral reservoir. The Panel recommends rapid initiation of ART (defined as initiating ART immediately or within days of HIV diagnosis) for all children who receive an HIV diagnosis. The urgency of rapid ART initiation is especially critical for children aged <1 year who carry the highest risk of rapid disease progression and mortality. However, it is worth noting that treatment of full-term infants aged ≤2 weeks and preterm infants is complex due to limited PK data and appropriate dosing of ARV drugs in this age group; this is an area of active investigation (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection).[63] In ART-naive children and adolescents with tuberculosis or cryptococcal meningitis, the Panel recommends initiation of treatment for the opportunistic infection first, ahead of ART initiation, with ART initiated within 2 to 8 weeks thereafter. However, appropriate timing of ART initiation in these cases should be discussed with a pediatric HIV specialist.

While ART is being initiated, it is important to assess and discuss issues associated with adherence with caregivers and, when developmentally appropriate, with children. Intensive follow-up during the first few weeks to months after ART initiation is also recommended to support the child and caregiver. Medication adherence is the core requirement for successful virologic control. The Panel recognizes that achieving consistent adherence in children is often challenging.[66,67] Incomplete adherence leads to loss of viral control and the selection of drug-resistant mutations, but forcibly administrating ARV drugs to younger children may result in treatment aversion, which often persists into adulthood. The need for lifelong therapy also can lead to treatment fatigue, which occurs during adolescence among many children with perinatally acquired HIV.[68]

The Panel believes the benefits of early ART initiation outweigh the potential risks and recommends rapid initiation of ART in all children with HIV, regardless of clinical, immunologic, or virologic status. However, individual clinical and/or psychosocial factors may lead patients, caregivers, and providers to make a collaborative decision to defer ART. When making the decision to defer ART, medical factors—such as the opportunity to limit seeding of the viral reservoir in newborns, the child's HIV disease stage,[69] and the presence of HIV-related signs and symptoms[70]—need to be balanced against any potential barriers to rapid ART initiation. If ART is deferred, the health care provider should continue to educate and work with the family to overcome barriers to treatment, as well as closely monitor the child's virologic, immunologic, and clinical status at least every 3 to 4 months **(AIII)** (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). Clinicians should initiate ART in children with HIV in whom treatment has been deferred when—

- HIV RNA levels increase,
- CD4 count or percentage values decline (e.g., approaching Centers for Disease Control and Prevention Stage 2 or 3),[69]
- The child develops new HIV-related clinical symptoms,[70] *or*
- The ability of a caregiver and child to adhere to the prescribed regimen improves.

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

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• The selection of an initial antiretroviral (ARV) regimen should be individualized based on several factors, including the characteristics of the proposed regimen, the patient's characteristics, drug efficacy, potential adverse effects, patient and family preferences, and the results of viral resistance testing **(AIII).** • For treatment-naive children, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends initiating antiretroviral therapy with three drugs: a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone plus an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor **(AI*).** • Table 7 below provides a list of Panel-recommended ARV regimens that are designated as *Preferred* or *Alternative*; recommendations vary by a patient's age, weight, and sexual maturity rating.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Criteria Used for Recommendations

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

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

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when available) with the drug or regimen, preferably in children, as well as adults;
- The extent of pediatric experience with a specific drug or regimen;

- The incidence and types of short-term and long-term drug toxicity in people who are taking the drug or regimen, focusing on toxicities that are reported in children;
- The availability and acceptability of formulations that are appropriate for pediatric use, including palatability, ease of preparation (e.g., syrups vs. powders), pill size, and the number of pills or volume of oral solution needed for an appropriate dose;
- Dosing frequency, and food and fluid requirements; *and*
- The potential for drug interactions with other medications.

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

- *Preferred:* Drugs or drug combinations are designated as *Preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and when pediatric studies using surrogate markers have demonstrated safety and appropriate drug exposure. Additional considerations are listed above.
- *Alternative:* Drugs or drug combinations are designated as *Alternative* for initial therapy when clinical trial data in children or adults show efficacy, but the drugs or drug combinations have disadvantages when compared with *Preferred* regimens. Drugs or drug combinations may be classified as *Alternative* for use in treatment-naive children if they are less effective or durable than a *Preferred* regimen in adults or children; if specific concerns exist about toxicity, dosing, formulation, administration, or interaction; or if experience with the use of these drugs or drug combinations in children is limited.

Factors to Consider When Selecting an Initial Regimen

An antiretroviral (ARV) regimen for children should generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an active drug from one of the following classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Choice of a regimen should be individualized based on several factors, including the characteristics of the proposed regimen; the patient's age, weight, sexual maturity rating (SMR), and other characteristics; and the results of drug-resistance testing.

Drug recommendations often include both age and weight limitations. Although age can be used as a rough guide, body weight (when available) is the preferred determinant for selecting a specific drug. An exception to this is infants aged <14 days. Many drugs that are recommended for use in very young infants do not have dosing recommendations for premature infants. Additional information regarding dosing recommendations in this population can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

The advantages and disadvantages of each regimen are described in detail in the sections that follow and in Table 8 below. Additional information regarding the advantages and disadvantages of specific drug combinations can be found in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. Specific information about the clinical efficacy, adverse events (AEs), and dosing recommendations for each drug can be found in Appendix A: Pediatric Antiretroviral Drug Information. In addition, clinicians should consider potential barriers to adherence. These barriers may include complex dosing schedules, food requirements, palatability problems, and the need to use multiple formulations to achieve an appropriate dose. Counseling patients and caregivers about adherence to therapy is essential for successful ART. The Panel recommends rapid initiation of ART (defined as initiating ART immediately or within days of diagnosis).

Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have antiviral activity and efficacy against hepatitis B virus (HBV) and should be considered for use in children with HBV/HIV coinfection. For a comprehensive review, see the Hepatitis B Virus,, Hepatitis C Virus, and Mycobacterium tuberculosis (TB) sections of the Pediatric Opportunistic Infection Guidelines.

Choosing an Initial Antiretroviral Regimen for Children with HIV

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

Clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a PI-based regimen for initial therapy. Three pediatric studies have compared an NNRTI-based regimen to a PI-based regimen, and results varied based on the age of the population studied and the specific drug used within the class.

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

in the LPV/r arm versus 76% in the NNRTI arm, a difference of 4% that was not statistically significant (95% confidence interval [CI], –9% to +17%).

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

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

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

Preferred initial regimens by age, weight, and drug class are shown in Figure 1 below. Additional information about *Preferred* initial regimens, *Preferred* NRTI backbones, *Alternative* initial regimens, and *Alternative* NRTI backbones are shown in detail in Table 7 below.

Integrase Strand Transfer Inhibitor-Based Regimens

Four INSTIs—BIC, DTG, elvitegravir (EVG), and RAL—are approved by the FDA for treating ARV-naive adults and children with HIV. INSTI-based regimens have quickly become the recommended regimens in adults due to their virologic efficacy, lack of drug interactions, and favorable toxicity profile. RAL is approved for the treatment of infants and children from birth onward with a weight of ≥2 kg. DTG is approved by the FDA for use in infants and children aged ≥4 weeks and weighing ≥3 kg. The FDC tablet BIC/FTC/TAF (Biktarvy) is approved by the FDA for use in children weighing ≥14 kg. EVG has been studied in adolescents in two FDC regimens and in combination with two NRTIs and ritonavir (RTV, r) boosting. BIC and DTG, the second-generation INSTIs, have higher barriers to resistance than the first-generation INSTIs RAL and EVG[10,11] and may have more activity against non-B subtypes of HIV.[12,13]

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

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

Bictegravir

BIC/FTC/TAF was approved by the FDA in 2018 for use in adults and in 2019 for use in children or adolescents weighing ≥25 kg. In October 2021, a lower strength formulation of BIC/FTC/TAF received FDA approval for use in children weighing ≥14 kg to <25 kg. BIC/FTC/TAF is approved for use in patients who are ART naive, and it also can be used to replace the current ARV regimen in patients who have been virologically suppressed (viral load <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known substitutions associated with resistance to the individual components of the FDC tablet.

BIC/FTC/TAF has been studied in adolescents (Cohort 1) aged 12 years to <18 years and weighing ≥35 kg and in two younger cohorts of children: Cohort 2, aged 6 years to <12 years who weighed ≥25 kg, and Cohort 3, aged ≥2 years and who weighed ≥14 kg to <25 kg. All participants had maintained viral loads <50 copies/mL for ≥6 months. Cohorts 1 and 2 received the adult formulation of BIC/FTC/TAF. Children in Cohort 3 received BIC 30 mg/FTC 120 mg/TAF 15 mg. Overall, the drug was well tolerated in all participants in all cohorts. Drug exposure in all cohorts was similar to the exposure observed in adults. At 24 weeks, all 50 adolescents and 50 children in Cohorts and 2 maintained viral suppression and at Week 48, 49 of 50 participants in each cohort maintained suppression.[14-18] Among children in Cohort 3, after 24 weeks, all 12 participants maintained viral suppression.[17,18]

Recommendation

- BIC/FTC/TAF is recommended as a *Preferred* INSTI-based regimen for children aged ≥2 years and weighing ≥14 kg **(AI*).** The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.

Dolutegravir

DTG is approved by the FDA for use in infants and children ≥4 weeks and weighing ≥3 kg. This recommendation is based on PK and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY), as well as a study of treatment-experienced (but INSTI-naive) older children.[9,19-21]

Early data from Botswana about the use of DTG around the time of conception showed a small significant increase in the prevalence of neural tube defects (NTDs) that has decreased over time.[17,22,2324] In the most recent analysis of data from this study, the prevalence of NTDs did not differ significantly between women receiving DTG and non-DTG regimens..[24] For additional information, refer to Teratogenicity, Recommendations for Use of Antiretroviral Drugs During Pregnancy, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers in the Perinatal Guidelines.

Recommendation

- DTG plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants, children, and adolescents aged ≥4 weeks and weighing ≥3 kg **(AI*)**. The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.[7,9,21,25,26]

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

Elvitegravir

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

Recommendation

- EVG/c/FTC/TAF is recommended as an *Alternative* INSTI-based regimen for children and adolescents weighing ≥25 kg who have creatinine clearance (CrCl) ≥30 mL/min **(AI*)**. The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and adolescent studies. The Panel does not recommend EVG/c/FTC/TAF as a *Preferred* INSTI-based regimen because EVG has a lower barrier to resistance compared with BIC or DTG and the potential for multiple drug–drug interactions from COBI.[27-31]

Raltegravir

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

Recommendation

- RAL plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants and children from birth to age 4 weeks who weigh ≥2 kg **(AI*).** It is an *Alternative* INSTI-based regimen for children aged ≥4 weeks due to its twice-daily dosing requirement and lower barrier to resistance compared with other INSTIs **(AI*).** The Panel bases this recommendation on data from randomized clinical trials in adults and pediatric studies that were performed largely in ARV-experienced children and adolescents.[7,32-40]
- Currently, the Panel **does not recommend** once-daily dosing of RAL for initial therapy in children and infants.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Doravirine (DOR; for children weighing ≥35 kg), EFV (for children aged ≥3 months), etravirine (ETR; for children aged ≥6 years), NVP (for children aged ≥15 days), and rilpivirine (RPV; for children aged ≥12 years) have been approved by the FDA for treatment of HIV infection in pediatric patients. NNRTIs have a long half-life that allows less frequent drug administration; a lower risk of dyslipidemia and fat maldistribution than some agents in the PI class; and, generally, a lower pill burden than PIs. However, a single viral mutation can confer high-level drug resistance to all NNRTIs except ETR, and cross-resistance to other NNRTIs is common. Rare, but serious and potentially life-threatening, skin and hepatic toxicity can occur with the use of all NNRTI drugs, but these AEs are most frequently observed in patients taking NVP, at least among adults with HIV. NNRTIs have the potential to interact with other drugs that are also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted-PI regimens. Table 8 below lists the advantages and disadvantages of using NNRTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information for each drug.

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

Doravirine

DOR is available both as a single-drug tablet and an FDC tablet that contains DOR 100 mg/3TC 300 mg/TDF 300 mg, marketed as Delstrigo. Efficacy studies in adults have demonstrated that DOR/3TC/TDF is noninferior to EFV-based regimens and darunavir (DRV)-based regimens. Virologic efficacy of DOR was similar in patients with higher viral loads >100,000 copies/mL as to those with viral loads ≤100,000 copies/mL. DOR, more so than EFV, compared favorably to the other drugs in these trials in terms of AEs (including better central nervous system tolerability) and is recommended as initial ART in adults with certain clinical situations. The FDC tablet has been studied in 45 adolescents aged 12 years to 17 years and weighing ≥45 kg. Of these adolescents, 43 were virologically suppressed and 2 were ART-naive. After 24 weeks of treatment, the regimen was well tolerated, with a low incidence of drug-related AEs (2.2%; 95% CI, 0.1–11.8). None of the AEs were serious or led to regimen discontinuation. HIV-1 RNA <50 copies/mL was demonstrated in all participants except for one ART-naive participant who met the criteria for virologic failure based on poor adherence to the study regimen. [44]

Recommendation

- DOR plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for initial treatment of HIV in children and adolescents weighing ≥35 kg **(BI*)**. The Panel bases this recommendation on data from studies that evaluated the efficacy and tolerability of this drug in adults,[41-43] as well as early findings from pediatric PK studies.[44]

Efavirenz

Although EFV dosing recommendations are available for patients aged ≥3 months and weighing ≥3.5 kg, the Panel does not endorse the use of this drug in infants and children aged 3 months to 3 years because the PKs of EFV in very young patients can be highly variable. There may be a role for use of EFV in children aged <3 years who have HIV and TB coinfection, because EFV is one of the few ARVs with minimal drug–drug interaction.[45]

Recommendation

- EFV plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for initial treatment of HIV in children aged ≥3 years **(AI*).** The Panel bases this recommendation on data from studies that evaluated the efficacy and tolerability of this drug in adults and children.[25,32,46-63]

Nevirapine

Extensive clinical and safety data exist for the use of NVP in children with HIV, and NVP has shown ARV efficacy when used as a component in a variety of combination regimens.[1,5,6,64-68] NVP also has been used extensively as prophylaxis for the prevention of HIV transmission in young infants during the peripartum period and during breastfeeding.[69] The safety and PKs of NVP have been studied at low doses used for prophylaxis. Less information is currently available from studies in very young infants about the safety and PKs of NVP at the higher doses required for treatment.

Early testing of infants allows HIV infection to be confirmed before 14 days of age. The Panel recommends the use of NVP as a *Preferred* NNRTI when a clinician plans to initiate treatment before age 14 days. Although early treatment initiation may limit the size of the viral reservoir,[70,71] no clinical trial data currently suggest that initiating treatment within the first 14 days of life improves outcomes compared to starting treatment after age 14 days (see When to Initiate Therapy in Antiretroviral-Naive Children). Clinicians should consult an expert in pediatric HIV infection when considering the use of NVP in infants aged <14 days. Additional considerations regarding the use of NVP in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Recommendation

- NVP plus a two-NRTI backbone is recommended as a *Preferred* NNRTI-based regimen in infants aged <14 days and as an *Alternative* NNRTI-based regimen for children aged ≥14 days to <3 years **(AI).** Clinicians should consider switching from NVP to LPV/r or RAL in children aged ≥14 days to <4 weeks because these drugs are the *Preferred* ARV agents for this age bracket. LPV/r has better clinical outcomes than NVP in children aged <3 years. The Panel recommends switching from NVP to LPV/r in these patients because NVP is associated with rare occurrences of significant hypersensitivity reactions, including Stevens-Johnson syndrome, and rare (but potentially life-threatening) instances of hepatitis. NVP also has a low barrier to resistance, and conflicting data exist about the virologic efficacy of NVP-based regimens compared to the efficacy of *Preferred* regimens.[1,5,6,66-68,72-79]

Rilpivirine

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

RPV also is available as an extended-release injectable suspension in a kit that contains an extended-release injectable cabotegravir (CAB) suspension. The two-drug regimen of injectable CAB and RPV is approved for treatment of HIV-1 infection in adults with viral suppression; it is not approved for initial therapy. This regimen is under study in adolescents.

Recommendation

- RPV plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for children and adolescents aged ≥12 years and weighing ≥35 kg who have HIV viral loads ≤100,000 copies/mL **(AI*).** The Panel bases this recommendation on the limited experience with RPV in adolescents and the larger body of evidence in adults.[53,80-83]

Protease Inhibitor-Based Regimens

Advantages of PI-based regimens include excellent virologic potency and a high barrier to drug resistance (because multiple mutations are required for a patient to develop resistance). However, because PIs are metabolized via hepatic enzymes, these drugs have the potential for multiple drug interactions. They also may be associated with metabolic complications, such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider when selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, the availability of palatable pediatric formulations, the drug interaction profile, the toxicity profile (particularly toxicities related to metabolic complications), the age of the child, and the availability of data regarding the use of the drug in children. Table 8 below lists the advantages and disadvantages of using PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

RTV is a potent inhibitor of the CYP3A4 isoenzyme and can be used in low doses as a PK booster when coadministered with some PIs, increasing drug exposure by prolonging the half-life of the boosted PI. Currently, only LPV/r is available as a coformulated product. In addition, the use of RTV boosting increases the risk of hyperlipidemia[84] and drug interactions. COBI is an alternative CYP3A4 inhibitor that also can be used as a booster. It is available in a single-drug tablet and in coformulations with atazanavir (ATV) and with DRV. Currently, the single-drug tablet is approved by the FDA for administration with ATV in children weighing ≥35 kg and for administration with DRV in children weighing ≥40 kg.

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

Atazanavir Boosted with Ritonavir or Cobicistat

ATV is a once-daily PI that was approved by the FDA in March 2008 for use in combination with a two-NRTI backbone in children aged ≥6 years. ATV is most often boosted with RTV. Approval was extended in 2014 for use in infants and children aged ≥3 months and weighing ≥5 kg.[85,86] ATV administered in combination with COBI has been approved by the FDA for use in adults (using the single-agent COBI tablet) and in children weighing ≥35 kg.

Recommendation

- ATV/r plus a two-NRTI backbone is recommended as an *Alternative* PI-based regimen for children aged ≥3 months **(AI*)**. ATV/c plus a two-NRTI backbone is an *Alternative* PI-based regimen for children weighing ≥35 kg. These regimens have been shown to be virologically potent in adult and pediatric studies and have been well tolerated in pediatric studies. However, the oral powder formulations of ATV and RTV and the oral solution formulation of RTV can be cumbersome to administer.[35,49,82,84,87-92]
- The Panel **does not recommend** the use of unboosted ATV.

Darunavir Boosted with Ritonavir or Cobicistat

DRV/r is approved by the FDA for use in ARV-naive and ARV-experienced children aged ≥3 years and weighing ≥10 kg. In addition, once-daily dosing of DRV/r is approved for ARV-naive children aged ≥3 years and weighing ≥10 kg, and for ARV-experienced patients who do not have DRV resistance-associated mutations. Once-daily dosing of DRV/r was investigated during a substudy of a twice-daily dosing trial in children aged 3 years to <12 years. This PK evaluation lasted only 2 weeks, after which the participants were switched back to the twice-daily regimen.[93] FDA dosing recommendations are based on PK models from this study, but this dose has never undergone trials for clinical efficacy in this age group. A more recent study also suggested that once-daily DRV/r dosing is acceptable for children and adolescents. In this study, the plasma concentration-time curve for DRV/r was substantially lower than the mean value observed in adults; however, trough levels were similar. Due to these findings, and because of the lack of more information about the efficacy of once-daily DRV/r dosing in ARV-naive and ARV-experienced children aged <12 years, the Panel recommends a twice-daily dose of DRV/r in children aged >3 years to <12 years.[94] DRV administered in combination with COBI has been approved by the FDA for use in adults (using the single-agent COBI tablet) and in children weighing ≥40 kg.[95]

Recommendation

- DRV/r plus a two-NRTI backbone is recommended as an *Alternative* PI-based regimen for children aged ≥3 years and weighing ≥10 kg **(AI*).** The Panel bases these recommendations on the virologic potency shown by DRV/r in adult and pediatric studies, and this combination's high barrier to the development of drug resistance and excellent toxicity profile in adults and children.[35,96-103]
- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of an *Alternative* PI-based regimen in ARV-naive children and adolescents weighing ≥40 kg **(AI*).**
- Twice-daily dosing of DRV/r should be used for children aged ≥3 years to <12 years.
- Twice-daily dosing of DRV/r should be used when the following DRV resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- DRV/c plus a two-NRTI backbone is recommended as an *Alternative* PI-based regimen for adolescents aged ≥12 years and weighing ≥40 kg who are not sexually mature.

Lopinavir/Ritonavir

LPV/r is approved to treat HIV infection in infants and children with a postmenstrual age ≥42 weeks and postnatal age ≥14 days. Once-daily LPV/r dosing is approved by the FDA for initial therapy in adults,[104] but PK data in children do not support a recommendation for once-daily dosing.[105,106]

Recommendation

LPV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days to <4 weeks **(AI)** and as an *Alternative* PI-based regimen in children aged ≥4 weeks **(AI*).** This regimen has been shown to be virologically potent in adult and pediatric studies and has been well tolerated in pediatric studies. Although it is recommended only as a *Preferred* PI-based regimen for a narrow age range, use of LPV/r is supported by many Panel members as a *Preferred* PI-based regimen in children up to 3 years of age due to extensive experience with this drug and ease of administering a liquid formulation in infants and very young children.[25,51,87,88,96,104-111]

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

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. The advantages and disadvantages of the different dual-NRTI backbone options that are recommended for initial therapy in children are listed in Table 8 below.[14,31,59,89,112-116]

See What Not to Start for more information. Also, see Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

In the dual-NRTI backbones listed below, 3TC and FTC are interchangeable. Both 3TC and FTC are well tolerated and have few AEs. FTC is similar to 3TC and can be substituted for 3TC as one component of a *Preferred* dual-NRTI backbone (i.e., FTC used in combination with ABC, TDF, or zidovudine [ZDV]). The main advantage of FTC over 3TC is that it can be administered once daily as part of an initial regimen. Both 3TC and FTC select for the M184V resistance mutation, which is associated with high-level resistance to both drugs, a modest decrease in susceptibility to ABC, and improved susceptibility to ZDV and TDF as a result of decreased viral fitness.[117,118]

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

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

Abacavir in Combination with Lamivudine or Emtricitabine

ABC is approved by the FDA for use in children aged ≥3 months when administered as part of an ARV regimen. ABC also has been reported to be safe in infants and children aged ≥1 month. More recently, an ABC dosing recommendation using PK simulation models has been endorsed by the World Health Organization using weight-band dosing for full-term infants from birth to 1 month of age. Based on this endorsement, the Panel recommends ABC from birth in full-term infants testing negative for the HLA-B5701 allele.[119,120]

Recommendation

- ABC plus 3TC or FTC is recommended as the *Preferred* dual-NRTI combination for children aged ≥3 months **(AI)** and for full-term infants from birth **(BIII)**. A negative test for the HLA-B5701 allele should be obtained prior to starting ABC regardless of age.
- Studies of adults and children have reported virologic efficacy and favorable toxicity profiles for these combinations.[33,121-128] Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on the safety of ABC in infants when initiated at age <3 months.[129-131] Additional information about the use of ABC between birth and 1 month of age can be found in the Appendix A: Pediatric Antiretroviral Drug Information. Due to ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed before administration of ABC.
- Once-daily dosing is recommended when using the pill formulation of ABC. Twice-daily dosing of liquid ABC is recommended for initial therapy; a change to once-daily dosing can be considered for clinically stable patients with undetectable viral loads and stable CD4 counts.[132-135]

Tenofovir Alafenamide in Combination with Emtricitabine

TAF is an oral prodrug of tenofovir. It is approved by the FDA as a component of an FDC tablet that also contains EVG, COBI, and FTC for the treatment of HIV in ARV-naive individuals weighing ≥25 kg who have an estimated CrCl ≥30 mL/min. Additional safety and PK data are available for children aged 6 years to <12 years who are receiving this FDC tablet.[30] TAF formulated as an FDC tablet with FTC and BIC is FDA approved for use in children weighing ≥14 kg (see Bictegravir).[14,136] An FDC tablet that contains FTC/TAF (Descovy) is available for use in children weighing ≥14 kg, with dosage determined by a child's weight. In January 2022, the FDA approved a lower strength formulation of the FTC/TAF FDC tablet for use in children weighing ≥14 kg to <25 kg.[137]

Coadministration of TAF with boosted ATV, DRV, or LPV increases TAF exposure to concentrations that are higher than those seen with use of EVG/c/FTC/TAF. Because no data exist on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with

COBI-boosted or RTV-boosted PIs in children weighing <35 kg cannot be assured and is not recommended.

Recommendation

- FTC/TAF is recommended as a *Preferred* dual-NRTI combination in children and adolescents weighing ≥14 kg with estimated CrCl ≥30 mL/min when used with an INSTI or NNRTI. FTC/TAF is a *Preferred* dual-NRTI combination when used with a PI in children and adolescents weighing ≥35 kg who have estimated CrCl ≥30 mL/min **(AI*).** FTC/TAF also is recommended as a *Preferred* drug combination when used in the regimen BIC/FTC/TAF for children and adolescents weighing ≥14 kg **(AI*).** EVG/c/FTC/TAF is recommended as an *Alternative* drug regimen for children and adolescents weighing ≥25 kg **(AI*).** The Panel makes these recommendations because TAF has a lower risk of renal and bone AEs than TDF.
- FTC/TAF is neither approved by the FDA nor recommended for use in combination with a boosted PI in children weighing <35 kg, because this combination has not been adequately studied in this age and weight group.

Tenofovir Disoproxil Fumarate in Combination with Lamivudine or Emtricitabine

TDF is approved by the FDA for use in children and adolescents aged ≥2 years when administered as part of an ARV regimen. Decreases in bone mineral density (BMD) have been observed in adults and children receiving TDF, but the clinical significance of these decreases is unknown.[113-116,140,141] Before starting treatment, clinicians should consider whether the benefits of using TDF outweigh the potential risk of decreased BMD.[142]

Recommendation

- TDF plus 3TC or FTC is recommended as an *Alternative* dual-NRTI combination for children aged ≥2 years to 12 years **(AI*).** The Panel bases this recommendation on the virologic efficacy and ease of dosing of these combinations.[113-116,122-125,143-148]

Zidovudine in Combination with Abacavir

In a European pediatric study, patients who received ZDV plus ABC had lower rates of viral suppression and a greater number of toxicities that led to regimen modification than in patients who received ABC plus 3TC.[112,121] Recent data from the IMPAACT P1106 trial and two observational cohorts provide reassuring data on the safety of ABC in infants when initiated at age <3 months.[129-131]

Recommendation

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

Zidovudine in Combination with Lamivudine or Emtricitabine

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

Recommendation

- ZDV plus 3TC or FTC is recommended as a *Preferred* dual-NRTI combination for infants and children from birth to age ≤1 month, and as an *Alternative* combination in children aged ≥1 month and adolescents **(AI*).** Twice-daily dosing is required for all ages with ZDV. Other NRTIs that require only once-daily dosing in children aged ≥6 years are available.[126,149-151]
- In children aged ≥6 years and adolescents who are not sexually mature (i.e., those with SMRs of 1–3), the Panel recommends ZDV plus 3TC or FTC as an *Alternative* dual-NRTI combination **(BII).**

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

<table>
<tr><th></th><th colspan="5">Patient Age and Weight Class</th></tr>
<tr><th></th><th>Birth to <14 Days of Age[a,b,c]</th><th>Aged ≥ 14 Days and ≥ 2 kg to < 4 Weeks</th><th>Aged ≥ 4 Weeks and ≥ 3 kg to <2 Years</th><th>Aged ≥ 2 Years and ≥ 14 kg</th><th>Aged ≥ 6 Years and ≥ 25 kg</th></tr>
<tr><th rowspan="3">INSTI-Based Regimens</th><td colspan="2">Two NRTIs plus RAL[c]</td><td colspan="3"></td></tr>
<tr><td colspan="3"></td><td colspan="2">Two NRTIs plus BIC[d]</td></tr>
<tr><td colspan="2"></td><td colspan="3">Two NRTIs plus DTG[e]</td></tr>
<tr><th>NNRTI-Based Regimens</th><td>Two NRTIs plus NVP[a,f]</td><td colspan="4"></td></tr>
<tr><th>PI-Based Regimens</th><td></td><td>Two NRTIs plus LPV/r[b]</td><td colspan="3"></td></tr>
</table>

[a] Preferred NRTIs are listed in Table 7 below.

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

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

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

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

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

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

Key: BIC = bictegravir; DTG = dolutegravir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide

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

An antiretroviral (ARV) regimen for treatment-naive children is generally made up of a two–nucleoside reverse transcriptase inhibitor (NRTI) backbone and either one non-nucleoside reverse transcriptase inhibitor (NNRTI) **or** one integrase strand transfer inhibitor (INSTI) **or** one protease inhibitor (PI) boosted with ritonavir or cobicistat (COBI). Regimens are designated *Preferred* based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens also have demonstrated efficacy, but clinical experience with these regimens is limited, or these regimens are more difficult to administer than *Preferred* regimens. Regimens should be tailored to the individual patient by weighing the advantages and disadvantages of each combination. Many agents have multiple formulations and age and weight recommendations. Refer to Appendix A: Pediatric Antiretroviral Drug Information for additional information and recommended doses and formulations (also see Table 8 below). In addition, many drugs that are recommended for use in newborns do not have dosing recommendations for premature infants. Additional information regarding dosing recommendations in this population can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

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

Preferred Initial Regimens Based on Age and Weight at Time of Treatment Initiation			
Age	**Weight Restriction**	**Regimens**	**FDC Available (see Appendix A, Table 1)**
Newborns, Birth to Age <14 Days[a,b]	None	Two NRTIs **plus** NVP	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Neonates ≥14 Days to Age <4 weeks	None	Two NRTIs **plus** LPV/r[b]	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Infants and children Aged ≥4 Weeks	≥3 kg	Two NRTIs **plus** DTG[d] Two NRTIs **plus** DTG[d]	No Yes (≥25 kg)
Children Aged ≥2 Years	≥14 kg	Two NRTIs **plus** BIC[e]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs			
Age	**Dual-NRTI Backbone Options**		**FDC Available**
Neonates Aged Birth to 1 Month	ABC **plus** (3TC **or** FTC)[f]		No[g]
	ZDV **plus** (3TC **or** FTC)[h]		No[g]
Infants and children Aged >1 Month to <2 Years	ABC **plus** (3TC **or** FTC)[f]		Yes
	ABC **plus** (3TC **or** FTC)[f]		Yes

Children and Adolescents Aged ≥2 Years with SMRs of 1–3	FTC/TAF[i] in children and adolescents weighing ≥14 kg and receiving a regimen that contains an INSTI or an NNRTI FTC/TAF[i] in children and adolescents weighing ≥35 kg and receiving a regimen that contains a boosted PI		Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Regimens Based on Age and Weight at Time of Treatment Initiation			
Age	**Weight Restriction**	**Regimens**	**FDC Available**
Neonates, infants, and children Aged ≥14 Days to <3 Years	None	Two NRTIs **plus** NVP[j]	No
Infants and children Aged ≥4 Weeks to <3 Months	None	Two NRTIs **plus** LPV/r[b]	No
	≥2 kg	Two NRTIs **plus** RAL[c]	No
Infants and children Aged ≥3 Months to <3 Years	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** DRV/r[k]	No
	None	Two NRTIs **plus** EFV[l]	No[g]
	None	Two NRTIs **plus** LPV/r[b]	No
	≥25 kg	Two NRTIs **plus** EVG/c[m]	Yes
	≥35 kg	Two NRTIs **plus** DOR[n]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	None	Two NRTIs **plus** ATV/r	No
	None	Two NRTIs **plus** DRV/r[k]	No
	None	Two NRTIs **plus** EFV[l]	Yes
	None	Two NRTIs **plus** LPV/r[b]	No
	None	Two NRTIs **plus** RAL[c]	No
	≥25 kg	Two NRTIs **plus** EVG/c[m]	Yes
	≥35 kg	Two NRTIs **plus** ATV/c[o]	No
		Two NRTIs **plus** DOR[n]	Yes
		Two NRTIs **plus** RPV[p]	Yes
	≥40 kg	Two NRTIs **plus** DRV/c[q]	Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Dual-NRTI Backbone Options for Use in Combination with Other Drugs			
Age	**Dual-NRTI Backbone Options**		**FDC Available**
Infants and children Aged ≥1 Month to <6 Years	ZDV **plus** (3TC **or** FTC)[h]		No[g]
	ZDV **plus** ABC[f]		No
Children Aged ≥2 Years to 12 Years	TDF **plus** (3TC **or** FTC)[r]		Yes

Children and Adolescents Aged ≥6 Years and SMRs of 1–3	ZDV **plus** (3TC **or** FTC)[h]	Yes
	ZDV **plus** ABC[f]	No

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

[b] In general, LPV/r **should not be administered** to neonates before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days (see the Lopinavir/Ritonavir section in Appendix A: Pediatric Antiretroviral Drug Information). Some experts would choose not to start with LPV/r as a *Preferred* initial regimen in neonates aged ≥14 days to <4 weeks but would choose to start with NVP instead.

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

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

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

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

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

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

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

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

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

[l] EFV is approved by the FDA for use in children aged ≥3 months and weighing ≥3.5 kg, but it **is not recommended** by the Panel for initial therapy in children aged ≥3 months to 3 years. FDC tablets that contain EFV/FTC/TDF (Atripla) and EFV 600 mg/3TC/TDF (Symfi) are available. See the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information for information about use of the FDC EFV 400 mg/3TC/TDF (Symfi Lo).

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

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

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

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

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

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

Key: 3TC = lamivudine; ABC = abacavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for *Initial* Therapy in 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.

ARV Class/ Agent(s)	Advantages	Disadvantages
All INSTIs	**INSTI Class Advantages** • Few drug–drug interactions • Well tolerated	**INSTI Class Disadvantages** • Limited data on pediatric dosing or safety • Possible weight gain in adults, especially Black/African American women
BIC	Once-daily administration Can give with or without food Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	The FDC tablet **is not recommended** for patients with hepatic impairment or an estimated CrCl <30 mL/min. The FDC tablet **should not be coadministered** with rifampin or dofetilide.
DTG	Once-daily administration Can give with food Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets) Single-agent DTG pills are available in several doses and are small in size. DTG is available as dispersible tablets for suspension.	Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing of DTG CNS side effects, particularly sleep disturbances. Early concerns about a possible increased risk of NTDs in infants born to women who were receiving DTG at the time of conception have decreased substantially. The Panel for Antiretroviral Guidelines for Adults and Adolescents and the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission include DTG among the preferred ARV agents for use in people of childbearing potential and for use in people who are pregnant or are trying to conceive. Risks and benefits should be discussed to support informed decision making, see Dolutegravir, Appendix C: Antiretroviral Counseling Guide for Health Care Providers.
EVG	Once-daily administration Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	Among INSTIs, EVG has the lowest barrier to the development of resistance. If EVG is coadministered with COBI, the potential exists for multiple drug interactions because COBI is metabolized by hepatic enzymes (e.g., CYP3A4). COBI inhibits tubular secretion of creatinine, and this may result in increased serum creatinine but normal glomerular clearance.
RAL	Can give with food Available in tablet, chewable tablet, and powder formulations	Potential for rare systemic allergic reaction or hepatitis Granule formulation requires a multistep preparation before administration; caregiver must be taught how to properly prepare this formulation.

ARV Class/ Agent(s)	Advantages	Disadvantages
	Chewable tablets can be crushed and mixed with various liquids for infants ≥4 weeks of age who weigh ≥3 kg. Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥40 kg.	
All NNRTIs	**NNRTI Class Advantages** • Long half-life • Lower risk of dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking the solid formulation; easier to use and adhere to than PI-based regimens	**NNRTI Class Disadvantages** • A single mutation can confer resistance, with cross-resistance between EFV and NVP. • Rare, but serious and potentially life-threatening, cases of skin rash (including SJS) and hepatic toxicity. All NNRTIs pose this risk, but the risk is greatest with NVP; these toxic effects have not been reported in neonates. • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4). Information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker
DOR	Once-daily administration Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets) Can be taken with or without food Has continued antiviral activity in the setting of some NNRTI mutations	Neuropsychiatric AEs, but fewer than reported for EFV DOR is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers, see Doravirine. Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours after a fixed-dose combination of DOR/3TC/TDF or an increase of the DOR dose to 100 mg twice daily, see Doravirine.
EFV	Once-daily administration Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets) Potent ARV activity Can give with food (but avoid high-fat meals) Capsules can be opened and added to food.	Neuropsychiatric AEs (bedtime dosing is recommended to reduce CNS effects) Rash (generally mild) No commercially available liquid formulation Limited data on dosing for children aged <3 years No data on dosing for children aged <3 months
NVP	Liquid formulation is available. Dosing information for young infants is available. Can give with food 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

ARV Class/ Agent(s)	Advantages	Disadvantages
		Twice-daily dosing necessary in children with BSA <0.58 m^2 Low barrier to resistance
RPV	Once-daily dosing Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	Should not use in patients with viral loads >100,000 copies/mL Must be taken with a ≥500 kcal meal at a consistent time each day; this may affect adherence. Low barrier to resistance
All PIs	**PI Class Advantages** • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well-documented. • Resistance to PIs requires multiple mutations. • When combined with a dual-NRTI backbone, a regimen that contains a PI targets HIV at two steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.	**PI Class Disadvantages** • Metabolic complications, including dyslipidemia, fat maldistribution, and insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI-based or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence • Most PIs require RTV boosting, resulting in drug interactions that are associated with RTV.
Boosted ATV	Once-daily dosing Powder formulation is available. ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).	No liquid formulation Should be administered with food Indirect hyperbilirubinemia is common, but asymptomatic. Scleral icterus may be distressing to the patient, which may affect adherence. Must be used with caution in patients with preexisting conduction system defects (can prolong the PR interval of an ECG) RTV is associated with a large number of drug interactions.
Boosted DRV	Can be used once daily in children aged ≥12 years Liquid formulation is available. DRV requires a boosting agent. Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	Pediatric pill burden high with current tablet dose formulations Should be administered with food Must be boosted to achieve adequate plasma concentrations Contains sulfa moiety. The potential for cross-sensitivity between DRV and other drugs in sulfonamide class is unknown. RTV is associated with a large number of drug interactions. Can be used only once daily in the absence of certain PI-associated resistance mutations.

ARV Class/ Agent(s)	Advantages	Disadvantages
LPV/r	LPV is only available coformulated with RTV in liquid and tablet formulations. Tablets can be given without food, but they may be better tolerated when taken with a meal or snack.	Poor palatability of liquid formulation (bitter taste) Liquid formulation should be administered with food. RTV is associated with a large number of drug interactions. Should not be administered to neonates before a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) and a postnatal age ≥14 days Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of an ECG)
ABC plus (3TC or FTC)	Palatable liquid formulations Can give with food Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC.
FTC/TAF for children aged ≥6 years	Once-daily dosing Small tablet size Lower risk of TFV-associated renal and bone toxicity with TAF than with TDF in adults Available in FDC tablets (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets)	Limited data on the safety and efficacy of this combination in children Increased lipid levels
TDF plus (3TC or FTC) for adolescents with SMRs of 4 or 5	Once-daily dosing for TDF Resistance is slow to develop. Lower risk of mitochondrial toxicity than other NRTIs Can give with food 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)	Limited pediatric experience Potential bone and renal toxicity Appropriate dosing is complicated by numerous drug–drug interactions with other ARV agents, including ddI, LPV/r, ATV, and TPV.
ZDV plus (3TC or FTC)	Extensive pediatric experience Coformulations of ZDV and 3TC are available (Combivir and generic) for children weighing ≥30 kg. Palatable liquid formulations Can give with food FTC is available as a palatable liquid formulation that can be administered once daily.	Bone marrow suppression and lipoatrophy with ZDV ZDV requires twice-daily dosing.

ARV Class/ Agent(s)	Advantages	Disadvantages
ZDV plus ABC	Palatable liquid formulations Can give with food	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC. Bone marrow suppression and lipoatrophy with ZDV ZDV requires twice-daily dosing.

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

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What Not to Start: Regimens Not Recommended for Use in Antiretroviral-Naive Children

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

This section describes antiretroviral (ARV) drugs and drug combinations that either are not recommended for use in ARV-naive children or lack sufficient data to recommend their use in ARV-naive children. Although many ARV agents and combinations are available, some are not recommended for use as part of an initial regimen in ARV-naive children, but they may be used in ARV-experienced children (see Recognizing and Managing Antiretroviral Treatment Failure). Several ARV drugs that are no longer available or recommended for use in children for several years have been removed from this chapter, including the nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and didanosine; the protease inhibitors (PIs) indinavir, nelfinavir, saquinavir, tipranavir (TPV), and fosamprenavir; and the fusion inhibitor enfuvirtide (see Archived Drugs in Appendix A: Pediatric Antiretroviral Drug Information). The PI ritonavir is no longer recommended for use as the sole PI in an ARV regimen but is used at a reduced dose as a pharmacokinetic (PK) enhancer (boosting agent) with other ARV drugs (e.g., atazanavir, darunavir).

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) classifies ARV drugs and drug combinations that are not recommended for use in ARV-naive children into one of three categories:

- *Not Recommended for Initial Therapy:* These include ARV drugs and drug combinations that are not recommended for initial therapy in ARV-naive 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. These drugs and drug combinations are listed in Table 9, and selected drugs or drug combinations are discussed below.
- *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, these drugs and drug combinations may be appropriate to consider when managing treatment-experienced children (see Management of Children Receiving Antiretroviral Therapy). These drugs also are listed in Table 9, and selected drugs or drug combinations are discussed below.
- *Antiretroviral Drug Regimens That Are Never Recommended:* Several ARV drug and drug combinations should never be used in children or adults. They are summarized in Table 10. Clinicians also should be aware of the components of fixed-dose combination (FDC) tablets so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Antiretroviral Drugs and Drug Combinations Not Recommended for Initial Therapy in Children

Atazanavir Without Ritonavir or Cobicistat Boosting

Although unboosted atazanavir (ATV) is approved by the U.S. Food and Drug Administration (FDA) for use in treatment-naive adolescents—aged ≥13 years and weighing ≥40 kg—who are unable to tolerate ritonavir (RTV), data from the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)/Pediatric AIDS Clinical Trials Group (PACTG) 1020A study indicate that adolescents require higher doses of unboosted ATV (as measured by milligram per meter squared of body surface area) than adults to achieve adequate drug concentrations.[1] The Panel **does not recommend** using ATV without RTV boosting because of these findings.

Regimens That Contain Only Nucleoside Reverse Transcriptase Inhibitors

In adult trials, regimens that contain only NRTIs have shown less potent virologic activity than non-nucleoside reverse transcriptase inhibitor (NNRTI)–based or PI-based regimens.[2,3] Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited to small observational studies.[4,5] In a study on the use of the triple-NRTI regimen abacavir plus lamivudine (3TC) plus zidovudine in ARV-experienced children, this combination showed evidence of only modest viral suppression; only 10 of the 102 children had viral loads of <400 copies/mL at Week 48 of treatment.[6] Therefore, regimens that contain only NRTIs **are not recommended** for treatment-naive or treatment-experienced children.

Regimens That Contain Three Drug Classes

The Panel **does not recommend** using regimens that contain agents from three drug classes as initial regimens (e.g., an NRTI plus an NNRTI plus a PI or an integrase strand transfer inhibitor plus an NRTI plus a PI or NNRTI). Although studies of regimens that contain three classes of drugs have demonstrated that these regimens are safe and effective in ARV-experienced children and adolescents, these regimens have not been studied as initial regimens in treatment-naive children and adolescents. These regimens also have the potential to induce resistance to three drug classes, which could severely limit future treatment options.[7-11] Ongoing studies are investigating the use of drugs from three drug classes to treat neonates.

Regimens That Contain Three Nucleoside Reverse Transcriptase Inhibitors and a Non-Nucleoside Reverse Transcriptase Inhibitor

Current data are insufficient to recommend using a regimen that contains three NRTIs plus an NNRTI in young infants. A review of nine cohorts from 13 European countries suggested that this four-drug regimen produced responses that were superior to the responses observed in patients receiving boosted-PI regimens or three-drug NRTI regimens.[12] There has been speculation that poor tolerance and poor adherence to a PI-based regimen may account for some of the differences. The AntiRetroviral Research for Watoto (ARROW) trial, conducted in Uganda and Zimbabwe, randomized 1,206 children (with a median age of 6 years) to receive either a standard NNRTI-based, three-drug regimen (two NRTIs and one NNRTI) or a four-drug regimen (three NRTIs and one NNRTI). After a 36-week induction period, the children on the four-drug regimen continued treatment on a regimen that contained two NRTIs plus one NNRTI or a three-NRTI regimen. Although improvements in CD4 T lymphocyte (CD4) cell counts were observed at Week 36 (with a percentage change of approximately 14.4% in the four-drug arm compared with 12.6% in the three-drug arm), these benefits were not sustained after patients switched to the three-drug regimens for the duration of the study. Furthermore, no differences in viral suppression rates were observed between the two arms at Week 36.[13] Because three-drug regimens have been shown to be effective and well tolerated and because efficacy data are lacking for the four-drug regimen, the Panel **currently does not recommend** the four-drug regimen.

Antiretroviral Drugs and Combinations with Insufficient Data to Recommend for Initial Therapy in Children

Several ARV drugs and drug regimens are not recommended for use as initial therapy in ARV-naive children or for specific age groups because of insufficient pediatric data. In some cases, new agents have shown promise in adult clinical trials but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. In addition, some dosing schedules may not be recommended in certain age groups because of insufficient data. As new data become available, these agents may become recommended agents or regimens, as summarized below and also listed in Table 9.

Cabotegravir with or Without Rilpivirine for Oral or Intramuscular Injections

In 2021, the FDA approved long-acting injectable (LAI) formulations of cabotegravir (CAB), a novel INSTI, and the NNRTI rilpivirine (RPV) for the treatment of HIV infection in adults to replace a current, stable ARV regimen in patients with no prior history of treatment failure and no known or suspected resistance to CAB or RPV who have demonstrated sustained viral suppression (e.g., 3–6 months). These two LAI ARVs are copackaged together and marketed as Cabenuva. An oral lead-in with the oral formulations of the ARVs for at least 28 days is recommended to assess tolerability. The LAI formulations can then be administered on a monthly or an every 2 month schedule in adults. Clinical trials in adolescents are ongoing and planned for younger children. At this time, the Panel **does not recommend** the use of this LAI regimen for children.

Darunavir with Low-Dose Ritonavir-Based Regimens Administered Once Daily for Children Aged ≥3 Years to <12 Years

Whereas modeling studies identified a once-daily dosing schedule for darunavir/ritonavir (DRV/r) that is now approved by the FDA, the Panel is concerned about the lack of direct PK studies for this approach in individuals aged ≥3 years to <12 years. Therefore, the data are not sufficient to recommend once-daily dosing for initial therapy in this age group. For children aged ≥3 years to <12 years, twice-daily DRV/r is a *Preferred* drug combination. For older children who have undetectable viral loads while receiving a twice-daily DRV/r-based regimen, practitioners can consider switching to once-daily DRV/r dosing if no DRV-associated resistance mutations are present. Once-daily dosing helps support adherence by making this drug combination easier to use.

Efavirenz-Based Regimens for Children Aged ≥3 Months to 3 Years

EFV is approved by the FDA for use in children aged >3 months and weighing ≥3.5 kg. An EFV-based regimen has been shown to have variable PKs in studies of the very young; because of this, the Panel does not recommend using EFV in children aged <3 years at this time (see the Efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information). When the use of EFV is being considered for children aged <3 years, cytochrome P450 (CYP) 2B6 genotyping should be performed, if available, to predict a patient's metabolic rate for EFV. Therapeutic drug monitoring also can be considered. Additionally, EFV in children <3 years may be considered in the setting of HIV/tuberculosis coinfection, because EFV is one of the few ARVs with minimal drug–drug interactions seen with other ARVs and rifampin.[14]

Etravirine-Based Regimens

Etravirine (ETR) is an NNRTI that has been studied in treatment-experienced children aged ≥1 years and is approved now by the FDA for use in children aged ≥2 years and weighing ≥10 kg.[15-17] ETR is associated with multiple interactions with other ARV drugs, including TPV/ritonavir, ATV/ritonavir, and unboosted PIs, and must be administered twice daily. The use of ETR likely will not be studied in treatment-naive children.

Fostemsavir-Containing Regimens

Fostemsavir (FTR) is a HIV-1 glycoprotein (gp120)-directed attachment inhibitor that is not approved for use in pediatric patients. FTR was approved by the FDA in 2020 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are failing their current ART regimen due to resistance, intolerance, or safety considerations. A PK and safety study of FTR in children and adolescents ≥20 kg (PENTA Foundation: NCT04648280) will soon be open to enrollment. At this time, the Panel **does not recommend** FTR as part of an initial treatment regimen for HIV-1 infection in children.

Ibalizumab-Containing Regimens

Ibalizumab (IBA) is a humanized IgG4 monoclonal antibody that binds to CD4 extracellular domain 2 and prevents conformational changes in the CD4-HIV envelope gp120 essential for viral entry, thereby blocking HIV entry into CD4 cells.[18] It was approved for use in adults with HIV-1 infection who are heavily pretreated, have multi drug-resistant virus, and are experiencing treatment failure. IBA has an orphan drug designation exempting the requirement for pediatric studies under the Pediatric Research Equity Act. At this time, because there is no experience with IBA in children, the Panel **does not recommend** its use as initial treatment for HIV-1 infection.

Maraviroc-Based Regimens

Maraviroc (MVC) is an entry inhibitor approved by FDA for use in children weighing ≥2 kg who have CCR5-tropic HIV-1. It has been used infrequently in children. A recent dose-finding study administered both the liquid and tablet formulations of MVC to treatment-experienced children aged 2 to 18 years who were grouped into four age cohorts.[19] The initial dose was based on body surface area and scaled from the recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP3A4 inhibitor or inducer.[19] A recent study of MVC in newborns at risk of HIV acquisition and weighing at least 2 kg established a dosing protocol that achieved target exposures and was deemed safe. No apparent differences in PK parameters were observed among infants of mothers with exposure to EFV and those without. None of the infants had HIV infection, nor were they receiving potent P450 CYP3A inhibitors.[20] As an entry inhibitor, MVC is under study in intensive treatment trials because of its hypothetical potential to limit the establishment of cell-associated viral reservoirs. However, MVC has several features that limit its role for routine uses, including multiple drug interactions, the need to be administered twice daily, and the fact that tropism assays must be performed prior to its use to ensure the presence of only CCR5-tropic virus. For those reasons, MVC **is not recommended** by the Panel for first-line treatment for neonates or older children.

Two-Drug Regimens

Increasing evidence suggests that in adults two-drug/two-class ARV regimens can be used in patients who have achieved and sustained viral suppression on a three-drug ART regimen. In general, adults who have had viral suppression for at least 3 to 6 months and with known susceptibility to the ARVs in the two-drug regimen have success after switching to these regimens. Regimens that demonstrated efficacy in adult clinical trials include DTG plus RPV, DTG plus 3TC or FTC, and boosted DRV plus DTG. At this time, no data support this strategy in children, and it **is not recommended** by the Panel.

Table 9. Antiretroviral Regimens or Components That Are Not Recommended for Initial Treatment of HIV Infection in Children and Adolescents

ARV Regimen	Rationale
Regimens containing only **NRTI**s	Inferior virologic efficacy
Regimens containing three drug classes	Potential to induce multiclass resistance Use as an initial regimen in children has not been studied
Regimens containing three **NRTI**s and one **NNRTI**	Added cost and complexity outweighs any benefit
Full-dose, dual-**PI** regimens	Insufficient data to recommend; potential for added toxicities
Regimens containing only two ARVs	Not FDA approved for pediatric use
ARV Component	**Rationale**
Unboosted **ATV-**containing regimens in children	Inadequate drug exposure
CAB	Not FDA approved for use in ARV-naive adults or for pediatric use
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
FTR	Not FDA approved for use in ARV-naive adults or for pediatric use
IBA	Not FDA approved for use in ARV-naive adults 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

Key: ARV = antiretroviral; ATV = atazanavir; CAB = cabotegravir; DRV = darunavir; DRV/r = darunavir/ritonavir; FDA = U.S. Food and Drug Administration; EFV = efavirenz; ETR = etravirine; FTR = fostemsavir; GI = gastrointestinal; IBA = ibalizumab; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate

Table 10. Antiretroviral Regimens or Components That Are Never Recommended for Treating HIV in Children and Adolescents[a]

ARV Regimen or Component	Rationale	Exceptions
One ARV Drug Alone (Monotherapy)	Rapid development of resistance Inferior antiviral activity compared with regimens that include ≥3 ARV drugs Monotherapy "holding" regimens are associated with more rapid CD4 count declines than nonsuppressive ART.	Infants with perinatal HIV exposure and negative virologic tests who are receiving 4–6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	Rapid development of resistance Inferior antiviral activity compared with regimens that include ≥3 ARV drugs	**Not recommended** for initial therapy Some clinicians may opt to continue using two NRTIs alone in patients who achieve virologic goals with this regimen.
Any Regimen Containing Both 3TC plus FTC	Similar resistance profile and no additive benefit	**No exceptions**
Any Regimen Containing Both TDF and TAF	No data to support potential additive efficacy or toxicity	**No exceptions**
Dual-NNRTI Combinations	Enhanced toxicity	**No exceptions**
TDF plus ABC plus (3TC *or* FTC) as a Triple-NRTI Regimen	High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults	**No exceptions**
NVP as component of Initial ARV Therapy regimen in Adolescent Girls with CD4 Counts >250 cells/mm³ or Adolescent Boys with CD4 Counts >400 cells/mm³	Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	Only if benefit clearly outweighs risk

[a] Several ARV drugs that are no longer available or that have not been recommended for use in children for several years have been removed from this chapter, including the NRTIs stavudine and didanosine; the protease inhibitors fosamprenavir indinavir, nelfinavir, saquinavir and tipranavir, and; and the fusion inhibitor enfuvirtide (see Archived Drugs).

Key: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection

Updated: Dec.30, 2021
Reviewed: Dec.30, 2021

Panel's Recommendations

• All newborns who were exposed perinatally to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI).**
• Newborn ARV regimens administered at doses that are appropriate for the infant's gestational age should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery **(AII).**
• A newborn's ARV regimen should be determined based on maternal and infant factors that influence the risk of perinatal transmission of HIV **(AII).** The uses of ARV regimens in newborns include the following:
  ○ **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.
  ○ **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns who are at highest risk of perinatal acquisition of HIV. Presumptive HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV, but it also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
  ○ **HIV Therapy:** The administration of a three-drug ARV regimen at treatment doses (called antiretroviral therapy [ART]) to newborns with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children).
• A 4-week zidovudine (ZDV) ARV prophylaxis regimen can be used in newborns whose mothers received ART during pregnancy and had viral suppression within 4 weeks prior to delivery (defined as a confirmed HIV RNA level <50 copies/mL) and for whom maternal adherence is not of concern **(BII).**
• Newborns at high risk of perinatal acquisition of HIV should begin presumptive HIV therapy (see Table 12 for recommended regimens). Newborns at high risk of HIV acquisition include those born to people with HIV who—
  ○ Have not received antepartum ARV drugs **(AI),** *or*
  ○ Have received only intrapartum ARV drugs **(AI),** *or*
  ○ Have received antepartum ARV drugs but who did not achieve viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks of delivery **(AII),** *or*
  ○ Have primary or acute HIV infection during pregnancy **(AII).**
• Presumptive HIV therapy should be administered to infants of mothers who have primary or acute HIV infection while breastfeeding **(AII).**
• If a patient presents with unknown HIV status and has a positive expedited HIV test during labor or shortly after delivery, the infant should begin presumptive HIV therapy **(AII).** If supplemental maternal testing is negative, the infant's ARV regimen should be discontinued **(AII).**
• For newborns with HIV infection, ART should be initiated **(AI).**
• The use of ARV drugs other than ZDV, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of the lack of dosing and safety data **(BII).**

• Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

All newborns with perinatal exposure to HIV should receive antiretroviral (ARV) drugs during the neonatal period to reduce the risk of perinatal HIV transmission, with selection of the appropriate ARV regimen guided by the level of transmission risk. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Maternal viral load is the most important risk factor for HIV transmission to a newborn. Newborns are at an increased risk for transmission when their mothers do not receive antiretroviral therapy (ART) during pregnancy, when mothers start antepartum treatment late in pregnancy, or when antepartum treatment does not result in viral suppression (defined as a confirmed HIV RNA level <50 copies/mL). Higher maternal viral load, especially in late pregnancy, correlates with higher risk of transmission. A spectrum of transmission risk depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis because it primarily focused on protection against newborn perinatal acquisition of HIV. More recently, clinicians have begun to identify newborns at highest risk for HIV acquisition and initiate three-drug ARV regimens as presumptive treatment of HIV. In this section, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without documented HIV infection to reduce the risk of HIV acquisition. ARV prophylaxis includes administration of a single agent—usually zidovudine (ZDV)—as well as combinations of two or three ARV drugs.
- **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. Presumptive HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but it also serves as ARV prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV Therapy:** The administration of a three-drug ARV regimen to newborns with documented HIV infection (see Diagnosis of HIV Infection in Infants and Children).

The terms ARV prophylaxis and presumptive HIV therapy describe the clinician's intent when prescribing ARV drugs, which may lead to an overlap between these two terms. For example, a presumptive HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (or sometimes three-drug) ARV prophylaxis regimens, notably those that use prophylactic doses rather than therapeutic doses of nevirapine (NVP), are not considered presumptive HIV therapy.

The interval during which newborn ARV prophylaxis or presumptive HIV therapy can be initiated and still be beneficial is undefined; however, most studies support providing ARV drugs as early as possible after delivery.[1-6]

Table 11 provides an overview of neonatal ARV management recommendations according to the risk of perinatal HIV transmission to the newborn, and Table 12 summarizes the recommendations for ARV drug dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks' gestational age), can be found in the Pediatric Antiretroviral Guidelines. Information about infants born to people with HIV-2 infection is available in HIV-2 Infection and Pregnancy and Table 11. In addition, the National Perinatal HIV Hotline (1-888-448-8765) is a federally funded service that provides free clinical consultation on difficult cases to providers who are caring for pregnant people with HIV and their newborns, and consultants can provide referrals to local or regional pediatric HIV specialists.

Table 11. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (1-888-448-8765).

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	Mothers who received ART during pregnancy with viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery and no concerns related to adherence	ZDV for 4 weeks[a]
High Risk of Perinatal HIV Transmission[a,b]	Mothers who did not receive antepartum ARV drugs Mothers who received only intrapartum ARV drugs Mothers who received antepartum ARV drugs but did not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should immediately discontinue breastfeeding**)[c]	Presumptive HIV therapy using either ZDV, 3TC, and NVP (treatment dose) *or* ZDV, 3TC, and RAL administered from birth up to 6 weeks[d]
Presumed Newborn HIV Exposure	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum	ARV management as described above for newborns with a high risk of perinatal HIV transmission

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
	or Mothers whose newborns have a positive HIV antibody test	Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV.
Newborn with HIV[e]	Positive newborn HIV virologic test/NAT	Three-drug ARV regimen using treatment doses. Refer to the What to Start in the Pediatric Antiretroviral Guidelines for specific treatment recommendations.

[a] ZDV prophylaxis regimen is recommended for infants born to mothers with HIV-2 mono-infection, see HIV-2 Infection and Pregnancy. If the mother has HIV-1 and HIV-2 infection, the infant ARV regimen should be based on the determination of low or high risk of HIV-1 transmission as described in the above table. Because HIV-2 is not susceptible to NVP, RAL should be considered for infants at high risk of perinatal HIV-2 transmission. See text for evidence that supports the use of presumptive HIV therapy and a two-drug ARV prophylaxis regimen.

[b] See Intrapartum Care for People with HIV for guidance on indications for scheduled cesarean delivery and intrapartum intravenous ZDV to reduce the risk of perinatal HIV transmission for mothers with an elevated viral load at delivery.

[c] Most Panel members would opt to administer presumptive HIV therapy to infants whose mothers had acute HIV during pregnancy because of the higher risk for *in utero* transmission. If acute HIV is diagnosed during breastfeeding, the mother should immediately discontinue breastfeeding.

[d] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications—such as 3TC, RAL, or NVP—may need to be administered for 2 to 6 weeks; the recommended duration for these drugs varies depending on infant HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim infant HIV NAT results. The two-drug regimen used in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–HIV Prevention Trials Network (HPTN) 040/Pediatric AIDS Clinical Trials Group (PACTG) 1043 for infants who were at a high risk for HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

[e] Infant ART should be initiated without waiting for the results of confirmatory HIV NAT testing, given the low likelihood of a false-positive HIV NAT. However, the specimen for confirmatory HIV testing should be obtained prior to ART initiation.

Note: ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 hours of delivery. See Table 12 for dosing specifics.

Key: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; NAT = nucleic acid test; NVP = nevirapine; Panel = Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 12. Antiretroviral Drug Dosing Recommendations for Newborns[a]

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
ZDV	ZDV administered for 4 weeks at the doses listed below.
Newborns at High Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	ZDV administered for 6 weeks, with no increase to the 12-mg/kg dose unless the infant has confirmed HIV infection (see ZDV dosing recommendations below). Dosing for 3TC, NVP, and RAL is described below.
Newborns with HIV Infection	
Recommended Regimen	**Lifelong Duration Recommended[b]**
Refer to Pediatric Antiretroviral Guidelines for specific treatment recommendations.	Lifelong therapy in accordance with current treatment guidelines. The ARV regimen should be individualized based on the infant's age and clinical determinants. Refer to the Pediatric Antiretroviral Guidelines for specific treatment recommendations.

Drug	Drug Doses by Gestational Age at Birth
ZDV **Note:** For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.	**≥35 Weeks' Gestation at Birth** *Birth to Age 4 Weeks:* • ZDV 4 mg/kg per dose orally twice daily *Age >4 Weeks:* • ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection. **Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks' Gestation from Birth to 4 Weeks** **Weight Band** — **Volume of ZDV 10 mg/mL Oral Syrup Twice Daily** 2 to <3 kg — 1 mL 3 to <4 kg — 1.5 mL 4 to <5 kg — 2 mL
	≥30 to <35 Weeks' Gestation at Birth *Birth to Age 2 Weeks* • ZDV 2 mg/kg per dose orally twice daily *Age 2 Weeks to 6 to 8 Weeks* • ZDV 3 mg/kg per dose orally twice daily *Age >6 to 8 Weeks* • ZDV 12 mg/kg per dose orally twice daily; make this dose increase only for infants with confirmed HIV infection.

	<30 Weeks' Gestation at Birth *Birth to Age 4 Weeks* • ZDV 2 mg/kg per dose orally twice daily *Age 4 to 8 to 10 Weeks* • ZDV 3 mg/kg per dose orally twice daily *Age >8 to 10 Weeks* • ZDV 12 mg/kg per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection
ABC[c] **Note**: ABC is not approved by the FDA for use in neonates and infants aged <1 month. However, dosing recommendations have been modeled using PK simulation.	**≥37 Weeks' Gestation at Birth** *Birth to 1 Month:* • ABC 2 mg/kg per dose orally twice daily *Age 1 Month to <3 Months:* • ABC 4 mg/kg per dose orally twice daily
3TC	**≥32 Weeks' Gestation at Birth** *Birth to Age 4 Weeks* • 3TC 2 mg/kg per dose orally twice daily *Age >4 Weeks* • 3TC 4 mg/kg per dose orally twice daily
NVP[d]	**≥37 Weeks' Gestation at Birth** *Birth to Age 4 Weeks* • NVP 6 mg/kg per dose orally twice daily *Age >4 Weeks* • NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.
	≥34 to <37 Weeks' Gestation at Birth *Birth to Age 1 Week* • NVP 4 mg/kg per dose orally twice daily *Age 1 to 4 Weeks* • NVP 6 mg/kg per dose orally twice daily *Age >4 Weeks* • NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.
	≥32 to <34 Weeks' Gestation at Birth *Birth to Age 2 Weeks* • NVP 2 mg/kg per dose orally twice daily *Age 2 to 4 Weeks* • NVP 4 mg/kg per dose orally twice daily *Age 4 to 6 Weeks* • NVP 6 mg/kg per dose orally twice daily *Age >6 Weeks*

	• NVP 200 mg/m^2 BSA per dose orally twice daily; only make this dose increase for infants with confirmed HIV infection.
RAL **Note:** If the mother has taken RAL 2 to 24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24 to 48 hours after birth; additional ARV drugs should be started as soon as possible.[7]	**≥37 Weeks' Gestation at Birth and Weighing ≥2 kg[e]** *Birth to Age 6 Weeks*

Body Weight	Volume (Dose) of RAL 10 mg/mL Suspension
Birth to 1 Week: Once-Daily Dosing	**Approximately 1.5 mg/kg per dose**
2 to <3 kg	0.4 mL (4 mg) once daily
3 to <4 kg	0.5 mL (5 mg) once daily
4 to <5 kg	0.7 mL (7 mg) once daily
1 to 4 Weeks: Twice-Daily Dosing	**Approximately 3 mg/kg per dose**
2 to <3 kg	0.8 mL (8 mg) twice daily
3 to <4 kg	1 mL (10 mg) twice daily
4 to <5 kg	1.5 mL (15 mg) twice daily
4 to 6 Weeks: Twice-Daily Dosing	**Approximately 6 mg/kg per dose**
3 to <4 kg	2.5 mL (25 mg) twice daily
4 to <6 kg	3 mL (30 mg) twice daily
6 to <8 kg	4 mL (40 mg) twice daily

[a] The optimal duration of presumptive HIV therapy in newborns who are at a high risk for perinatal HIV transmission is unknown. If possible, newborns who are at a high risk for HIV acquisition should receive ZDV for 6 weeks. Additional medications—such as 3TC, RAL, or NVP—may need to be administered for 2 to 6 weeks; the recommended duration for these drugs varies based on infant HIV nucleic acid test (NAT) results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration because this decision should be based on case-specific risk factors and interim infant HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a high risk for HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

[b] For ARV management after the first 6 weeks of life, see the Pediatric Antiretroviral Guidelines.

[c] ABC is approved by the FDA for use in children aged ≥3 months when administered as part of an ARV regimen. ABC also has been reported to be safe in infants and children ≥1 month of age. More recently, an ABC dosing recommendation using PK simulation models has been endorsed by the WHO using weight-band dosing for full-term infants from birth to 1 month of age.

See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for additional information about the use of ABC between birth and 1 month of age. At this time, the Panel does not recommend ABC as part of a presumptive HIV therapy regimen. However, in situations where ZDV is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV. This substitution should be considered in circumstances where increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. Because of ABC-associated hypersensitivity, negative testing for HLA-B5701 allele should be confirmed prior to administration of ABC.

[d] The NVP doses for infants ≥34 to <37 weeks gestation at birth and infants ≥37 weeks gestation at birth are not yet approved by the FDA. The FDA also has not approved a dose of NVP for infants aged <1 month. The doses for infants ≥32 to <34 weeks gestation at birth are based on modeling and might underestimate potential toxicity in infants of 32 to <34 weeks gestational age because the doses used to develop the model were lower than the doses now recommended. See the Two-Drug Antiretroviral Prophylaxis section in the text for prophylactic NVP dosing if using the NICHD-HPTN 040/PACTG 1043 prophylaxis regimen. See Nevirapine in Appendix A: Pediatric Antiretroviral Drug Information for additional information about dosing.

[e] RAL dosing is increased at 1 week and 4 weeks of age because metabolism by UGT1A1 is low at birth and increases rapidly during the next 4 to 6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth. In infants with HIV infection, twice-daily RAL can be replaced with once-daily DTG at ≥ 4 weeks of age (see Dolutegravir and What to Start in the Pediatric Antiretroviral Guidelines).

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BSA = body surface area; DTG = dolutegravir; FDA = U.S. Food and Drug Administration; IV = intravenous; NICHD-HPTN 040/PACTG 1043 = *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–HIV Prevention Trials Network 040/Pediatric AIDS Clinical Trials Group 1043; NVP = nevirapine; the Panel = the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission; PK = pharmacokinetic; RAL = raltegravir; UGT = uridine diphosphate glucotransferase; WHO = World Health Organization; ZDV = zidovudine

Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section and Table 11, the Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission (the Panel) presents available data and recommendations for management of newborns with documented HIV and newborns born to mothers who—

- Received antepartum ARV drugs and achieved effective viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery
- Are at high risk for transmitting HIV to their newborns, including mothers who—
  - Did not receive antepartum ARV drugs, *or*
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum ARV drugs but do not have effective viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery
- Had acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Achieved Viral Suppression on Antepartum Antiretroviral Drugs

The risk of HIV acquisition in newborns born to people who received ART during pregnancy and labor and who had undetectable viral load near or at the time of delivery is <1%. In the Pediatric AIDS Clinical Trials Group (PACTG) 076 study, ZDV alone reduced the incidence of perinatal HIV transmission by 66%, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent viral suppression during pregnancy.[8] The optimal minimum duration of neonatal ZDV prophylaxis has not been established in clinical trials. A 6-week ZDV regimen was studied in newborns in PACTG 076. However, the evidence that supports a reduced duration of ZDV prophylaxis in infants born to women who were suppressed virologically during pregnancy and at the time of delivery is mounting.[9-11] In the United Kingdom and many other European countries, a 2-week neonatal ZDV prophylaxis regimen is recommended for infants born to women who have a very low risk of HIV transmission. These women have been on ART for longer than 10 weeks **and** have had at least two documented maternal HIV viral loads <50 copies/mL at least 4 weeks apart **and** have viral loads <50 copies/mL at or after 36 weeks' gestation. A 4-week course of ZDV is recommended[12] if any of these criteria are not fulfilled but the maternal viral load is <50 copies/mL at or after 36 weeks' gestation. Compared with the 6-week ZDV regimen, 2 to 4 weeks on this regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.[13,14] The Swiss Federal Office of Public Health does not recommend infant ARV prophylaxis for infants of women with regular follow-up, ART use during pregnancy, and where maternal viral load is <50 copies/mL, ideally sustained throughout pregnancy, but at least at the last two consecutive measurements before delivery where viral load testing is performed at least 4 weeks apart and the last viral load is measured after week 36 of pregnancy.[15]

Currently, the Panel recommends a 4-week neonatal ZDV prophylaxis regimen for newborns if the mother achieved viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) on ART during pregnancy within 4 weeks of delivery and maternal adherence is not of concern. Some Panel members are supportive of the shorter 2-week ZDV regimen, as recommended by the British HIV Association and implemented in the United Kingdom and other European countries, in cases where there is very low risk of HIV transmission as defined above. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 12 shows recommended neonatal ZDV dosing based on gestational age and birthweight.

Newborns Born to Mothers Who Received No Antepartum Antiretroviral Drugs, Who Received Intrapartum Antiretroviral Drugs Only, Who Received Antiretroviral Drugs and Were Not Virally Suppressed Near Delivery, or Who Acquired HIV During Pregnancy or Breastfeeding

The Panel recommends that all newborns born to mothers who do not have viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) within 4 weeks prior to delivery, who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy are at high risk for HIV acquisition and **should receive presumptive HIV therapy**.[5,16-21] Primary or acute HIV infection during pregnancy also is associated with an increased risk of perinatal transmission of HIV. Infants born to people who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see Acute HIV Infection). The experience with these two strategies is described below.

Presumptive HIV Therapy

Early effective treatment of HIV infection in infants restricts the viral reservoir size, reduces HIV genetic variability, and modifies the immune response.[22-30] Because of these potential benefits of early ART, the Panel recommends a three-drug ARV presumptive HIV therapy regimen consisting of ZDV, lamivudine (3TC), and either NVP (at treatment dose) or raltegravir (RAL) for newborns at high risk of perinatal acquisition of HIV.

Although no clinical trials have compared the safety and efficacy of presumptive ART with single-drug or two-drug regimens, emerging data suggest that early presumptive HIV therapy has not been associated with serious adverse events. In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1115, 438 neonates who were at least 34 weeks gestational age at birth and enrolled within 48 hours of birth received a presumptive HIV therapy regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) (97% received ZDV and 3TC) and NVP dosed at 6 mg/kg twice daily for term neonates (≥37 weeks gestational age) or 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily therapy for preterm neonates (34 to <37 weeks gestational age). Among the study participants, 7% reported Division of AIDS (DAIDS) Grade 3 or 4 adverse events at least possibly related to ART. These Grade 3 or 4 events included 6% with neutropenia and 1% with anemia.[21] The Early Infant Treatment Study in Botswana initiated ART consisting of NVP 6 mg/kg twice daily, ZDV, and 3TC at <7 days gestational age in 40 infants who were ≥35 weeks gestational age and ≥2 kg at birth with HIV infection. Eighteen percent of these infants had Grade 3 or 4 hematologic toxicity, mostly neutropenia.[31] Similar findings have been reported from other smaller studies of presumed HIV therapy or early treatment of confirmed HIV infection.[31-33] In a prospective cohort in Thailand, infants who received a presumptive HIV therapy regimen that contained ZDV, 3TC, and NVP were more likely to have Grade 2 or higher anemia at 1 and 2 months of life compared with infants who received ZDV alone (48.5% vs. 32.3%; $P = 0.02$). However, no difference was found in the incidence of severe anemia (Grade 3) between the two groups.[34] Additionally, in a Canadian study, nonspecific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) that were potentially attributable to medication-related adverse effects were reported among the newborns who received presumptive HIV therapy but not among those who received ZDV only (10.2% vs. 0%; $P < 0.001$). Infants were more likely to discontinue presumptive HIV therapy prematurely than a regimen of ZDV alone (9.5% vs. 2.1%; $P = 0.01$).[33]

The Centers for Disease Control and Prevention recommends a three-drug ARV regimen for HIV-postexposure prophylaxis following occupational and nonoccupational HIV exposure. HIV acquisition risk in these circumstances is often lower than for newborns who are at high risk for HIV acquisition.[35,36] The pharmacokinetic (PK) and safety data of presumptive HIV therapy have provided reassuring evidence for its use in the neonatal period. Although the use of NVP to prevent perinatal HIV transmission has been found to be safe in neonates and newborns of low birthweight, these prophylaxis-dose regimens target trough drug levels that are at least 10-fold lower than targeted therapeutic levels. However, recent studies of therapeutic doses of NVP and RAL have established safe doses that achieve targeted PK parameters.[37-42]

At this time, if a presumptive HIV therapy regimen is required, the Panel recommends using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see Table 11 and Table 12). The optimal duration of presumptive HIV therapy in newborns at high risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if infant birth nucleic acid test (NAT) results are negative, whereas others would continue presumptive HIV therapy for 2 to 6 weeks depending on the risk of HIV transmission. In all cases, ZDV should be continued for 6 weeks. If HIV infection is confirmed and the infant is receiving NVP, NVP should be replaced with an integrase strand transfer inhibitor or a boosted protease inhibitor. Information about selecting an agent and recommended dosing can be found in What to Start in the Pediatric Antiretroviral Guidelines.

New dosing recommendations for abacavir (ABC) in neonates based on IMPAACT P1106 trial and two observational European and African cohorts are now available from the World Health Organization (WHO). ABC is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates and infants aged <3 months. However, a 2 mg/kg per dose twice-daily dose has been modeled using PK simulation and is endorsed by WHO using weight-band dosing for full-term infants from birth through 1 month of age. Limited observational data suggested safety of ABC when initiated in neonates <1 month of age (see Abacavir in the Pediatric Antiretroviral Guidelines). At this time, the Panel does not recommend ABC as part of a presumptive HIV therapy regimen. However, in situations where ZDV is not available or the infant has ZDV-associated toxicity, ABC could be considered an alternative to ZDV. This substitution should be considered in circumstances where increased risk of ZDV toxicity may exist, such as in infants with anemia or neutropenia. It also is suggested that negative testing for HLA-B5701 allele be confirmed prior to administration of ABC. Consulting an expert in pediatric HIV is recommended when selecting a therapy duration based on case-specific risk factors and interim HIV NAT results.[43-45]

Two-Drug Antiretroviral Prophylaxis

To date, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–HIV Prevention Trials Network 040/Pediatric AIDS Clinical Trials Group 1043 (NICHD-HPTN 040/PACTG 1043) trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at high risk of HIV acquisition.[5] In this study, 1,746 formula-fed infants born to women with HIV who did not receive any ARV drugs during pregnancy were randomized to receive one of three newborn prophylaxis regimens: the standard 6-week ZDV regimen; 6 weeks of ZDV plus three doses of NVP given during the first week of life (first dose given at birth or within 48 hours of birth, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of ZDV plus 2 weeks of 3TC plus nelfinavir (NFV).

Forty-one percent of the mothers received ZDV during labor. The risk of intrapartum transmission was significantly lower in the two-drug and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of ZDV alone; $P = 0.046$ for each experimental arm vs. ZDV alone).[5] The NICHD-HPTN 040/PACTG 1043 regimen was associated with NRTI resistance in 3 of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone and in 6 of 33 participants (18.2%) who were treated with ZDV plus NVP ($P > 0.05$). In addition, the third drug in the three-arm regimen was NFV, which has highly variable PKs in this age group and did not reach the NFV target plasma concentration in 46% of study participants.[46]

Although transmission rates with the two regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or ZDV-alone regimens (27.5% vs. 14.9% vs. 16.4%; $P < 0.001$ for both comparisons). For newborns who are at a high risk for HIV acquisition, the two-drug regimen used in NICHD-HPTN 040/PACTG 1043 is an option for preventing HIV transmission in infants aged ≥32 weeks' gestation with a birthweight of ≥1.5 kg. This two-drug regimen consists of 6 weeks of ZDV plus three doses of the prophylactic dose of NVP, with the NVP doses given within 48 hours of birth, 48 hours after the first dose, and 96 hours after the second dose. The prophylactic doses are NVP 12 mg per dose orally for infants weighing >2 kg and NVP 8 mg per dose orally for infants weighing 1.5 kg to 2 kg. **These are the actual doses, not the milligram per kilogram doses.** ZDV dosing is shown in Table 12.

Choosing Between Presumptive HIV Therapy and Two-Drug Antiretroviral Prophylaxis

Because a spectrum of transmission risk depends on maternal viral load and other maternal and infant factors **and** no randomized trials have compared the safety and efficacy of presumptive HIV therapy and two-drug ARV prophylaxis, experts have differing opinions about when to initiate presumptive HIV therapy and when to initiate two-drug prophylaxis. For instance, among people who received ARV drugs during pregnancy but who have a detectable viral load within 4 weeks prior to delivery, the level of maternal viremia that would prompt the use of a two-drug ARV prophylaxis regimen or presumptive HIV therapy is not definitively known.

In two large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had a viral load <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5 percent when viral load was 50 to 399 copies/mL and 2.8% and 4.1% when viral load was >400 copies/mL.[47,48] Although most Panel members would recommend initiating presumptive HIV therapy with any detectable level of viremia within 4 weeks prior to delivery, others may opt for a two-drug prophylaxis regimen if maternal viral load was less than 200 to 400 copies/mL. Emerging data about the lack of serious safety issues associated with presumptive HIV therapy in newborns is reassuring, even though mild-to-moderate adverse events may occur more frequently.

In summary, in scenarios where the infant is at high risk for HIV transmission, most Panel members recommend presumptive HIV therapy. In some situations, a two-drug ARV prophylaxis regimen may be considered (see Two-Drug Antiretroviral Prophylaxis in this section). Choosing between these regimens will depend on the clinician's assessment of the likelihood of HIV transmission, and a decision should be made after weighing the risks and benefits of the proposed regimen and discussing these transmission prevention strategies with the parents.

Consulting an expert in pediatric HIV or the National Perinatal HIV Hotline (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

Newborns Born to Mothers with Unknown HIV Status Who Present in Labor

Expedited HIV testing is recommended during labor for people with unknown HIV status; if testing is not performed during labor, it should be performed as soon as possible after birth for the mothers and/or their newborns (see Maternal HIV Testing and Identification of Perinatal HIV Exposure). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should begin presumptive HIV therapy immediately** without waiting for the results of supplemental tests. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit or special care or newborn nursery.

A positive initial test result in mothers or newborns should be presumed to indicate maternal HIV until supplemental testing clarifies maternal and newborn status. If appropriate test results for a mother (or newborn) are negative, newborn ARV drugs can be discontinued. Clinicians should be aware of their state laws because not all states allow HIV testing in infants without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should discontinue breastfeeding immediately until HIV is confirmed or ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.[49]

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns born to mothers with ARV drug-resistant virus is unknown. Although some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility,[50] perinatal transmission of multidrug-resistant virus does occur.[51-56] Whether resistant virus in the mother increases the antepartum/intrapartum risk of HIV acquisition by the infant also is unknown. A recently reported secondary analysis of data from the NICHD-HPTN 040/PACTG 1043 study demonstrated that the risk of perinatal transmission was not related to the presence of drug resistance mutations in mothers who had not received ARV drugs before the start of the study (adjusted odds ratio 0.8; 95% confidence interval, 0.4–1.5).[56] Maraviroc (MVC) was approved recently for infants ≥2 kg and may provide an additional treatment option for newborns of mothers carrying multidrug-resistant HIV-1 that remains CCR5-trophic.[57] However, the lack of data about MVC as prophylaxis or treatment in infants and the risk of drug interactions will limit its role for routine use in neonates. The ARV regimen for newborns born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery or through consultation via the National Perinatal HIV Hotline (1-888-448-8765). Additionally, no evidence exists that shows that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Newborns with HIV Infection

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and were intended to be as simple as possible for practical use. There was little reason to develop ARV regimens for the treatment of neonates because the long turnaround times to receive HIV NAT results meant that neonatal infections, in general, were not diagnosed during the first weeks of life. HIV NAT results are now available within a few days, and HIV in newborns is being diagnosed as early as the first days of life in many centers. A positive HIV NAT must be repeated to confirm HIV. However, ART initiation should not be delayed while waiting for the results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT. A confirmatory specimen should be obtained prior to ART initiation. To date, evidence that early treatment (before age 2 weeks) will lead conclusively to prolonged remission or better outcomes in newborns with HIV is lacking.

Information regarding the safety of early treatment of HIV in newborns has been reported from two studies. In the IMPAACT P1115 study, 54 infants with HIV began presumptive HIV therapy between 0.4 and 40 hours of life. Grade 3 or 4 related events—most of which were hematologic—occurred in 22 of 54 infants (41%) through 52 weeks of the study.[58] Forty infants with HIV in Botswana began treatment with NVP plus ZDV plus 3TC at a median age of 2 days (range 1–5 days) and transitioned to lopiniavir/ritonavir (LPV/r) plus ZDV plus 3TC at approximately 2 weeks of age. These infants had minimal toxicity during the first 12 weeks of treatment. Only one instance of Grade 3 neutropenia was reported, and no instances of Grade 3 or 4 anemia were reported.[31]

Earlier diagnosis of HIV in newborns and the increasing use of presumptive HIV therapy in newborns at high risk for HIV acquisition have necessitated the investigation of dosing and the safety of ARV drugs in term and preterm newborns. Although data are still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same, with the important exception of NVP (see the Pediatric Antiretroviral Guidelines).

Sufficient data exist to provide dosing recommendations for the treatment of HIV in neonates using the following medications (see the Pediatric Antiretroviral Guidelines):

- From birth in term and preterm newborns: ZDV, 3TC, NVP
- From birth in term newborns: emtricitabine, RAL, MVC, ABC
- From age 2 weeks in term newborns: LPV/r
- From age 4 weeks in term newborns: DTG

Dosing recommendations for **premature** newborns are available for ZDV, 3TC, and NVP only. Neonatal dosing advice—including dosing advice for premature newborns—is summarized in Table 12. For more detailed information about neonatal dosing recommendations and considerations when using these drugs, please see the Pediatric Antiretroviral Guidelines. Consultation with an expert in pediatric HIV is recommended to assist with management of infants born at <32 weeks gestation.

Newborns of Mothers Who Receive an HIV Diagnosis While Breastfeeding

People with suspected HIV (e.g., a positive initial screening test) should discontinue breastfeeding immediately until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding **is not recommended** for people with confirmed HIV in the United States, including those receiving ART (see Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed).[59]

The risk of HIV acquisition associated with breastfeeding depends on multiple newborn and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.[60] Newborns of people who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than those whose mothers have chronic HIV infection[61] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 count.[62]

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a mother with HIV (often because the mother just learned of her own HIV diagnosis) have yet to be defined. Some Panel members would consider the use of postexposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Postexposure prophylaxis, however, is less likely to be effective in this circumstance than with other nonoccupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than during a single exposure to the virus.[63]

Several studies of newborns who were breastfed by women with chronic HIV infection in low-resource settings have shown that a newborn's daily regimen of NVP, 3TC, LPV/r, or NVP plus ZDV can reduce the risk of postnatal infection during breastfeeding.[64-68] See Counseling and Managing Individuals with HIV in the United States Who Desire to Breastfeed for additional information. No trials have evaluated the use of multidrug regimens to prevent transmission after cessation of breastfeeding in mothers with acute HIV infection.

Given the higher risk of postnatal transmission from a person with acute HIV infection who is breastfeeding, an alternative approach favored by some Panel members is to offer presumptive HIV therapy until the infant's HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of presumptive HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for nonoccupational HIV exposure.[63] When making decisions about ARV management, clinicians should consult a pediatric HIV specialist and counsel the parents on the potential risks and benefits of a particular treatment strategy. The National Perinatal HIV Hotline (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

Newborns exposed to HIV during breastfeeding should be tested for HIV infection prior to initiating presumptive HIV therapy, as well as 4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding. An additional virologic test should be performed 2 to 4 weeks after discontinuing presumptive HIV therapy (see Diagnosis of HIV Infection in Infants and Children). If an HIV-exposed newborn is already receiving an ARV prophylaxis regimen other than presumptive HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV should be initiated. Resistance testing should be performed, and the ART should be modified if needed (see the Pediatric Antiretroviral Guidelines).

Short-Term Antiretroviral Drug Safety

Newborn prophylaxis with ZDV has been associated with only minimal toxicity, primarily transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see Initial Postnatal Management of the Neonate Exposed to HIV). Data on toxicities in newborns who were exposed to multiple ARV drugs are limited.

Other than ZDV, 3TC is the NRTI with the most clinical experience for neonatal prophylaxis. In early studies, neonatal exposure to combination ZDV/3TC therapy was limited, in general, to 1 week[19,69,70] or 2 weeks.[5] Six weeks of ZDV/3TC exposure in newborns also has been reported. These studies suggest that hematologic toxicity may be greater with ZDV/3TC than with ZDV alone, although the newborns in these studies also had *in utero* exposure to maternal HIV therapy that may have contributed to the toxicity.

In a French study, more cases of severe anemia and neutropenia were observed in newborns who were exposed to 6 weeks of ZDV/3TC prophylaxis plus maternal antepartum ZDV/3TC than in a historical cohort of newborns who were exposed only to maternal and newborn ZDV. Anemia was reported in 15% of newborns, and neutropenia was reported in 18% of newborns who were exposed to ZDV/3TC, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.[71] Similarly, in a Brazilian study of maternal antepartum ZDV/3TC and 6-week newborn ZDV/3TC prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia seen in 13% of newborns.[72]

Recent data from the IMPAACT P1106 trial and two observational European and African cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age, including infants with weight <3 kg.[73-75] See the Abacavir section of the Pediatric Antiretroviral Guidelines for additional information. At this time, the Panel suggests using ABC as an alternative to ZDV in certain situations and after negative HLA-B5701 allele testing.

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[76,77] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.[71,78-81]

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.[82] These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose NVP or the two-drug ZDV regimen plus three doses of NVP in the first week of life used in NICHD-HPTN 040/PACTG 1043 or in breastfeeding newborns receiving NVP prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.[5,64-66,68,83]

The FDA approved infant dosing of RAL for term neonates aged ≥37 weeks' gestation at birth and weighing ≥2 kg. Dosing information for RAL is not available for preterm or low-birthweight infants. PK modeling studies in infants with birthweight <2.5 kg with gestational age at birth ranging from 32.7 to 40 weeks suggests that prematurity reduces RAL clearance, and a modified dosing regimen may be needed to avoid elevated plasma RAL concentrations.[84] Infant RAL dosing needs to be increased at 1 week and 4 weeks of age. RAL is metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. In addition, bilirubin and RAL may compete for albumin binding sites, and extremely elevated neonatal plasma RAL concentrations could pose a risk of kernicterus.[40] IMPAACT P1110 is a Phase 1, multicenter trial that enrolled full-term neonates who were exposed to HIV and who were at risk for acquiring perinatal HIV-1 infection, with or without *in utero* RAL exposure. Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for ≤6 weeks from birth and followed for 24 weeks. Only one episode of Grade 4 neutropenia, possibly related to RAL, was reported. Among infants with RAL exposure (infants whose mothers received RAL within 2 to 24 hours before delivery), the first dose of RAL should be delayed for 24 to 48 hours after birth.[85] See the Raltegravir section of the Pediatric Antiretroviral Guidelines for additional information.

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Special Considerations for Antiretroviral Therapy Use in Adolescents with HIV

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• All adolescents with HIV should receive maximally suppressive antiretroviral (ARV) therapy; this is urgent for those who are sexually active, considering pregnancy, or pregnant **(AII).** • ARV regimen selection should include consideration of the adolescent's individual needs and preferences **(AIII).** See What to Start and Management of Children Receiving Antiretroviral Therapy for more information. • All adolescents with HIV should be screened for mental health disorders and substance use disorders **(AII).** • Reproductive health issues—including pregnancy intentions, contraceptive methods, safer sex techniques to prevent transmission of HIV and other sexually transmitted infections, pre-exposure prophylaxis for partners, pregnancy planning, and preconception care—should be discussed regularly **(AI).** • Providers should be aware of potential interactions between specific ARV medications and hormonal contraceptives that could lower contraceptive efficacy **(AII*).** • Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings **(AIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents.*

Background

The majority of individuals in the United States who acquired HIV through perinatal transmission are now adolescents or young adults. Most have had a long clinical course with an extensive antiretroviral (ARV) treatment history.[1,2] Many older youth and adults may have initially received nonsuppressive monotherapy or dual therapy prior to the availability of combination ARV regimens, including fixed-dose combination (FDC) formulations. Challenges that affect the treatment of adolescents with perinatally acquired HIV include extensive drug resistance, complex regimens, the long-term consequences of HIV and antiretroviral therapy (ART) exposure,[3] the developmental transition to adulthood, and psychosocial factors.[4-7]

In the United States, most adolescents aged ≥14 years who recently received HIV diagnoses acquired their infection by horizontal, rather than perinatal, transmission.[8] They generally follow a clinical course similar to that of adults, and the Adult and Adolescent Antiretroviral Guidelines should be consulted for treatment recommendations for these patients. Additional information that is specific to the care of post-pubertal adolescents can be found in Adolescents and Young Adults with HIV.

Timing and Selection of Antiretroviral Therapy

All adolescents with HIV (like all people with HIV) should initiate ART as soon as possible after HIV diagnosis. Recommendations for ART selection in adolescents with sexual maturity ratings (SMRs) between 1 and 3 can be found in What to Start and Appendix A: Pediatric Antiretroviral Drug Information. ART recommendations for adolescents and young adults with SMRs between 4 and 5 are available in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. Optimizing and simplifying treatment may be especially important when treating adolescents, because this can help improve adherence (see Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy). Clinicians who are treating adolescents of childbearing potential should consider additional factors before initiating ART, including potential drug interactions with contraception and the safety of using certain ARV drugs before conception or during pregnancy (see the Contraception, Pregnancy, and Antiretroviral Therapy section below).

Dosing of Antiretroviral Therapy for Adolescents with HIV

Clinical providers need to pay attention to the transition of adolescents from pediatric to adult ART dosing. Many ARV drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some protease inhibitors [PIs]) are administered to children at higher body weight–based doses or body surface area–based doses than would be predicted by direct extrapolation of adult doses. These doses are based on reported pharmacokinetic data that indicate more rapid drug clearance in children than in adults. Therefore, failure to ensure weight-appropriate dosing in adolescents can result in an increased risk of drug toxicity if higher pediatric dosing is not transitioned to lower adult dosing (often between 25 kg and 40 kg, depending on the particular drug).[9]

Adherence Concerns in Adolescents

Poor adherence to ART is a common problem among adolescents with HIV. Both psychosocial and cognitive developmental factors may contribute to adherence challenges, and these factors should be assessed regularly. The adolescent's individual needs and preferences also should be considered when making decisions about initiating or changing ART. Comprehensive systems of care are required to serve both the medical and psychosocial needs of adolescents with HIV, because they are frequently inexperienced with managing their health care and may also lack health insurance. Adolescents with perinatally acquired HIV infection are at risk for neurocognitive impairment, which also can interfere with medication adherence.[10] Many also are at risk for mental health comorbidities, including psychiatric, behavioral, and substance use disorders that may interfere with adherence to ART.[7,11] Compared with adults, youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow-up.[12,13] For further discussion of interventions to promote adherence in adolescents, see the Adolescents and Young Adults with HIV section of the Adult and Adolescent Antiretroviral Guidelines and a 2013 review by Agwu and Fairlie.[3]

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternatives to changing the ARV regimen can include, but are not limited to, simplifying treatment to a once-daily regimen or an FDC tablet; using cellphone alerts and other mHealth approaches to remind patients to take their medication and attend clinic visits; initiating a short-term deferral of treatment until adherence improves or while adherence-related problems (including mental health and substance use disorders) are aggressively addressed; initiating an adherence testing and training period during which a placebo (e.g., vitamin pill) is administered; scheduling appointments more frequently; employing directly observed therapy; and avoiding regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient's clinical and laboratory status monitored carefully. The use of long-acting oral and injectable ARV regimens for adolescents is currently being investigated. These regimens may provide an alternative approach for adolescents with adherence challenges.

Mental Health and Substance Use Concerns in Adolescents

Many factors can increase the risk of adverse mental health outcomes among adolescents with perinatally acquired HIV, including long-term medical treatment for a chronic disease, hospitalizations, stigma, the neurocognitive impacts of HIV, parental psychiatric and substance use disorders, and family and caregiver stress and loss. The prevalence of mental health disorders in youth with perinatally acquired HIV is high, with nearly 70% of these adolescents meeting the criteria for a psychiatric disorder at some point in their lives.[7,14-16] The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention deficit hyperactivity disorder. In at least one cohort, the risk of psychosis and severe chronic mental health disorders was higher in adolescents with perinatally acquired HIV than expected in the general young adult population.[17] Effectively managing psychiatric comorbidities can improve a patient's adherence to medical care, including ART, and can lead to better academic performance and interpersonal relationships (see Substance Use Disorders and HIV in the Adult and Adolescent Antiretroviral Guidelines).[11,18-20]

Interventions that address mental health in youth with perinatally acquired HIV include pharmacologic interventions; behavioral modification; and individual, family, and group counseling. The use of telehealth or counseling via videoconferencing may be feasible and acceptable and may improve access to mental health treatment for adolescents with HIV.[21] However, data are lacking on the effectiveness of these interventions on HIV clinical outcomes.[22-24] Current evidence suggests that a combination of tailored psychotherapy—such as cognitive behavioral therapy—and pharmacotherapy can reduce depressive symptoms in adolescents with HIV; however, clinicians who prescribe pharmacotherapy for depression must take potential interactions with ARV drugs into account.[25,26]

There is evidence that adolescents with perinatally acquired HIV are more likely to have substance use disorders compared to the general population.[27] However, available studies on substance use among adolescents with perinatally acquired HIV show age of initiation and rates of substance use similar to age-matched peers without HIV.[28] In a comparison of 390 youth with perinatal exposure to HIV versus 211 youth living with perinatally acquired HIV, investigators from the Pediatric HIV/AIDS Cohort Study (PHACS) found that nearly half of both groups had ever used alcohol or marijuana, with a majority having used either substance in the last 3 months, and one out of five marijuana users reporting at least daily use.[29] In another study, there was no difference in substance use between adolescents exposed to HIV and adolescents living with HIV. While rates of substance use may not be higher in adolescents with perinatally acquired HIV, the impact on health outcomes—including interference with medication adherence and increased risk taking and decreased safe sex practices—and the potential for comorbid mental health concerns make addressing substance use in adolescents with HIV an important consideration for HIV care providers.[30,31]

Providers who are caring for adolescents with HIV should incorporate screening for psychiatric and substance use disorders into routine care and refer patients to age-appropriate services as needed. The American Academy of Pediatrics policy statement provides some guidance and screening tools, particularly for depression. Screening tools for substance use—such as Screening, Brief Intervention, and Referral to Treatment (SBIRT) or Car, Relax, Alone, Forget, Friends, and Trouble (CRAFFT)—

may be used.[32] Providers also should consider emerging substance use trends when screening adolescents with HIV. Further guidance on screening tools for substance use and mental health is provided by the National Institute on Drug Abuse's Screening and Assessment Tools Chart.

Sexually Transmitted Infections in Adolescents

Clinicians should discuss the risk of sexually transmitted infections (STIs) with their patients. All adolescents with HIV should be screened for STIs and treated appropriately. Clinicians should regularly obtain a detailed sexual history for adolescents to determine which STI screening tests are appropriate. In young men who have sex with men, screening for STIs often requires sampling from several body sites—including the oropharynx, rectum, and urethra—because multiple sites of infection are common. Furthermore, a negative assay at a single site does not exclude infection at another site.[33] For a more detailed discussion of STIs, see the most recent Centers for Disease Control and Prevention guidelines,[34] Human Papillomavirus Disease in the Adult and Adolescent Opportunistic Infection Guidelines, and Human Papillomavirus in the Pediatric Opportunistic Infection Guidelines. All female adolescents with HIV who are sexually active should receive gynecologic services. All adolescents should receive three doses of the 9-valent human papillomavirus vaccination.

Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents with HIV may initiate sexual activity before or after puberty. Sexually active adolescents are at risk for unintended pregnancy. Approximately half of pregnancies in the United States, including those among women with HIV, are unintended or unplanned.[35,36] Providers should regularly assess adolescents' desires to become pregnant or avoid pregnancy (also known as their pregnancy intentions). Family planning counseling—including a discussion of the risks of sexual HIV transmission, perinatal HIV transmission, and methods for reducing these risks—should be provided to all youth. Reproductive health options—such as pregnancy planning, preconception care, contraceptive methods, pre-exposure prophylaxis for partners, the concept of Undetectable = Untransmittable (U=U),[37,38] and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of sexual HIV transmission—should be discussed regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use). For additional information, refer to the following sections of the Perinatal Guidelines: Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV and Reproductive Options When One or Both Partners Have HIV. The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.[39]

The possibility of planned and unplanned pregnancy should be considered when selecting an ARV regimen for a female adolescent. The most vulnerable period in fetal organogenesis is the first trimester, often before pregnancy is recognized. When treating adolescents of childbearing potential, clinicians should carefully review the potential toxicities of ARV drugs and consider making any necessary changes to a regimen as promptly as possible (e.g., before conception, when possible). For information about the selection and management of ARV drugs before and during pregnancy for people with HIV who are of childbearing age, see Table 5 in the Recommendations for Use of Antiretroviral Drugs During Pregnancy section of the Perinatal Guidelines. When discussing ART options with female adolescents and their caregivers, it is important to consider the benefits and risks of all ARV drugs and to provide the information and counseling needed to support informed decision-making (see Appendix C: Antiretroviral Counseling Guide for Health Care Providers).

Interactions Between Contraceptives and Antiretroviral Drugs

People living with HIV can use all available contraceptive methods, including hormonal contraceptives, implantable devices, intrauterine devices, the transdermal patch, and a vaginal ring.[40]

Several PIs and non-nucleoside reverse transcriptase inhibitors alter the metabolism of oral contraceptives, which theoretically may reduce the efficacy of oral contraceptive agents or increase the risk of estrogen-related or progestin-related adverse effects[41-43] (see Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker). Integrase strand transfer inhibitors appear to have no interaction with estrogen-based contraceptives.[44,45] For more information about potential interactions between ARV drugs and hormonal contraceptives, see Table 3 in the Perinatal Guidelines.

Concerns about loss of bone mineral density with long-term use of depot medroxyprogesterone acetate (DMPA), with or without coadministration of ART (specifically TDF), should not preclude the use of DMPA as an effective contraceptive, unless clinical evidence indicates bone fragility.

Pregnant Adolescents with HIV

Adolescents who want to become pregnant should receive preconception counseling and care, including a discussion of pregnancy planning and special considerations when using ARV drugs during pregnancy (see Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV in the Perinatal Guidelines). Pregnancy should not preclude the use of optimal therapeutic ARV regimens. Clinicians need to consider maternal and fetal safety, as well as the need to prevent perinatal transmission of HIV, when selecting regimens for pregnant people or adolescents who are planning to become pregnant. See the Prepregnancy Counseling and Care for Persons of Childbearing Age with HIV for more details about choosing an ARV regimen for pregnant people with HIV, including adolescents. Pregnancies occur as adolescents with perinatally acquired HIV enter adolescence and young adulthood.[46,47] Some studies suggest higher rates of adverse pregnancy outcomes—such as small-for-gestational-age infants—among pregnant people with perinatally acquired HIV than among those who acquired HIV by horizontal transmission. Unplanned pregnancy is not uncommon in youth living with perinatally acquired HIV.[47-49] Women with perinatally acquired HIV also may be more likely to have complex ARV histories, virologic failure, and drug resistance at the time of pregnancy.[50-52] However, the rate of perinatal transmission among pregnant people with perinatally acquired HIV who are receiving ART appears to be similar to the rate among people on ART who acquired HIV by horizontal transmission.[53-57]

Special Considerations for Adolescents with HIV Who Are Sexual Minorities

Adolescence represents a period of emerging recognition of sexual identity. Adolescents with HIV who are lesbian, gay, bisexual, transgender, or nonbinary require both culturally competent providers and tailored medical care. Health care providers should ask patients nonjudgmental questions about their sexual and gender identity to determine whether they require specific medical and support services. It is important to consider the possibility of drug–drug interactions in adolescents who are receiving both ART and gender-affirming hormone therapy. Additional resources for the care of these adolescents can be found in the Adolescents and Young Adults with HIV section and the Transgender People with HIV section of the Adult and Adolescent Antiretroviral Guidelines.

Transitioning Adolescents into Adult HIV Care Settings

Transition, as defined by Reiss et. al., may be described as "a multifaceted, active process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child- to the adult-focused health care system."[58] Facilitating a successful transition for adolescents with HIV from their pediatric/adolescent care clinic to adult care is important, but challenging.[59-62] Many adolescents disengage from care during the transition to adult care, putting them at risk for HIV progression and transmission to partners.[63-65] Pediatric and adolescent care providers and their multidisciplinary teams should have a formal written plan in place to transition adolescents to adult care. Although transition generally occurs when individuals are in their late teens or early 20s, discussion of and planning for the transition process should be initiated early in the teen years, with involvement from both the adolescent and their parents and/or caregivers. Care models for children and adolescents with perinatally acquired HIV tend to be family centered, consisting of a multidisciplinary team that often includes physicians, nurses, social workers, and mental health professionals. These providers generally have long-standing relationships with patients and their families, and care is rendered in discreet, intimate settings. Although expert care also is provided under the adult HIV care medical model, adolescents and their caregivers may be unfamiliar with the busier, more individual-centered clinics that are typical of adult medical care providers. These providers often expect patients to assume a greater level of responsibility for their care, and adolescents may be uncomfortable with providers with whom they do not have a long-standing relationship.

One multisite study in the United States found that adolescents who transitioned to adult care at an older age reported greater satisfaction with their care than those who transitioned at a younger age. Additionally, adolescents who reported being able to perform certain tasks that were related to their care (e.g., making appointments, requesting prescriptions, arranging transportation to appointments) were more likely to be engaged in adult care.[66] It may be beneficial to provide adolescents, caregivers, and their new adult medical care providers with support and guidance regarding the expectations for each person involved in the patient–provider relationship. In this situation, it may be helpful for a pediatric care provider and an adult care provider to share joint care of a patient for a period.

Adolescent care providers should have a candid discussion with the transitioning adolescent and their caregivers to understand what qualities the adolescent considers most important when choosing an adult care setting (e.g., confidentiality, small clinic size, low patient-to-provider ratio, availability of after-school or evening appointments). Social determinants—such as the patient's developmental status, behavioral/mental health comorbidities, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration—should be considered during transition.

No definitive model of transition to adult HIV care currently exists, and only a limited number of studies have reported on outcomes following transition, although research in this area is ongoing. However, emerging qualitative research has revealed the importance of the patient–provider relationship, including trust, the need for developmentally appropriate preparation for transition, and opportunities for growth and independence.[62,67] Recent studies have shown potential for successful transition and ongoing retention using models that include a multidisciplinary approach, which utilizes providers co-trained in both internal medicine and pediatrics, peer navigators, social workers, mental health support, and a youth-focused care model for adolescents who were already attending adult HIV clinics.[68,69]

Several studies have shown that youth with HIV who transitioned into adult care settings had higher rates of attrition from care than those who remained in pediatric/adolescent care; U.S. studies show that less than half of youth who transitioned care to an adult clinic remained in care after 9 to 12 months.[63,64,70] In addition to poor retention in care, several studies have identified poor viral suppression rates in transitioned youth and young adults with HIV.[2] Pre-transition virologic failure and longer linkage times have been associated with worse outcomes post-transition.[62,65] Furthermore, some reports from the United Kingdom suggest that the mortality rate of adolescents with HIV increases after transition,[19,65,71] underscoring the need to critically examine transition and determine the best mechanisms to optimize the long-term outcomes for youth with perinatally acquired HIV.[63]

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transition plans and who might benefit most from them.[60,72-79] To maximize the likelihood of success, providers should prepare adolescents for transition long before it occurs. Attention to the following key areas could improve retention in care and minimize the risk of ART interruptions:

- Educating HIV care teams and staff about transitioning;
- Beginning discussions about transition early, before the actual transition process;
- Developing a written, individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing communication between providers at pediatric/adolescent clinics and providers at adult clinics;
- Identifying adult care providers who are experts in providing care to adolescents and young adults;
- Fostering a trusting patient–provider relationship with new adult care providers;
- Addressing barriers caused by a lack of information, stigma, or disclosure concerns;
- Discussing the differences between the practice styles of adult clinics and pediatric/adolescent clinics;
- Helping youth develop the skills needed to manage their care, including counseling them on appointment management, the appropriate use of a primary care provider, the importance of prompt symptom recognition and reporting, and the importance of managing medications, insurance, and state and federal benefits;
- Identifying an optimal clinic model for a given setting (e.g., simultaneous transition of mental health and/or case management services versus a gradual phase-in);
- Clearly defining the desired outcomes for the transition, such as retention in care, ongoing access to other services (e.g., case management, mental health), clinical outcomes (e.g., viral suppression), and patient satisfaction;
- Implementing ongoing evaluations to measure the success of a transition model;
- Engaging in regular multidisciplinary case conferences between adult and adolescent care providers;
- Implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; *and*
- Identifying a care navigator who can provide support during the transition.

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Adherence to Antiretroviral Therapy in Children and Adolescents with HIV

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• Strategies to maximize adherence should be discussed before and/or at initiation of antiretroviral therapy (ART) and before changing regimens **(AIII).** • Adherence to therapy must be assessed and promoted at each visit, and strategies to maintain and/or improve adherence must be continually explored **(AIII).** • In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used **(AIII).** • Once-daily antiretroviral regimens and regimens with a low pill burden should be prescribed whenever feasible **(AII*).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *†Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression. Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, and subtherapeutic or partial dosing.[1,2] Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of resistance to one or more drugs in a given ARV regimen and possible cross-resistance to other drugs in the same class. Multiple factors—including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance—influence the adherence–resistance relationship.[3-5] In addition to compromising the efficacy of the current regimen, suboptimal adherence can limit the options for future effective ARV drug regimens in patients who develop multidrug-resistant HIV; it also can increase the risk of secondary transmission of drug-resistant virus.

Poor adherence to ARV drugs is commonly encountered in the treatment of children and adolescents with HIV. A variety of factors—including medication formulation, frequency of dosing, drug toxicities and side effects, and the child's age and developmental stage, as well as psychosocial, behavioral, and sociodemographic characteristics of children and caregivers—have been associated with inadequate adherence. However, no consistent predictors of either good or poor adherence in children have been identified.[6-8] Several studies have demonstrated that adherence is not static and can vary with time on treatment.[9] More recently, findings from the U.S. Pediatric HIV/AIDS Cohort Study (PHACS) demonstrated that the prevalence of nonadherence increased with age. Among 381 children and adolescents with perinatally acquired HIV, the prevalence of nonadherence increased from 31% to 50% ($P < 0.001$), and the prevalence of unsuppressed viral loads increased from 16% to 40% ($P < 0.001$) between pre-adolescence and late adolescence/young adulthood.[10] Similarly, in a report from the Early Pediatric Initiation Canada Cure Cohort, only 73% of the children initiated on ART maintained viral suppression 3 years after it was first achieved.[11] These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work with patients and their families to ensure that adherence education, support, and assessment are integral components of care.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by drug regimen, patient and family factors, and the patient–provider relationship.[12,13] Despite improvements over the last several years, the availability of once-daily and single-tablet ARV regimens and palatable formulations for infants and young children are limited.[14] Furthermore, infants and children are dependent on others for medication administration; adult caregivers may face barriers that undermine adherence in children, including forgetting doses, changes in routine, being too busy, and child refusal.[15,16] Caregivers also may be inadequately prepared to support their child's adherence. In a study of communication strategies among caretakers of children with perinatally acquired HIV in rural South Africa, many caregivers used coercion and threats of grave consequences of nonadherence as a communication strategy to enforce adherence.[17] Furthermore, some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.[18] Adherence also may be jeopardized by social and health issues within a family (e.g., substance use, poor physical or mental health, unstable housing, poverty, violence, involvement with the criminal justice system, limited social support).[19-22]

Adherence Assessment and Monitoring

Clinicians should begin assessing potential barriers to adherence and discussing the importance of adherence with patients before initiating or changing an ARV regimen. Evaluations should assess social and behavioral factors that may influence adherence and should identify individual needs for intervention. Clinicians should ask patients about their experience with taking medications, as well as concerns and expectations about treatment. Before beginning treatment, it is important that the patient explicitly agree to the treatment plan, which should include strategies to support adherence. It is also important to alert patients to potential adverse effects (AEs) of ARV drugs (e.g., nausea, headaches, abdominal discomfort, sleep disturbances), explain how they can be managed, and emphasize the importance of informing the clinical team if they occur.

A routine adherence assessment should be incorporated into every clinical visit. Adherence is difficult to assess accurately; different methods of assessment have yielded different results, and each approach has limitations.[23-25] Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals who are on ART (see Plasma HIV-1 RNA [Viral Load] and CD4 Count Monitoring in the Adult and Adolescent Antiretroviral Guidelines). It also can be used as positive reinforcement to encourage continued adherence.[26] In addition to viral load monitoring, clinicians should use at least one other method to assess adherence.[24] Table 13 below includes common approaches to monitoring medication adherence.

Strategies to Improve and Support Adherence

When concerns about adherence emerge, a patient should be seen and/or contacted frequently (by telephone, text message, email, and social networking as allowed within the context of local legal and regulatory requirements) to assess adherence and to determine the need for strategies that can improve and support adherence. During the first month of treatment (or a regimen change), a patient can be contacted weekly, or even daily, if necessary. The growing use of telemedicine visits, which allow remote and often face-to-face contact, provides new opportunities to support families and visualize ART handling/swallowing, as well as to conduct directly observed therapy (DOT) in the home setting (see Clinical and Laboratory Monitoring of Pediatric HIV Infection and Table 3).

Strategies should include simplifying the ARV drug regimen, developing treatment plans that integrate medication administration into daily routines (e.g., associating medication administration with daily activities, such as brushing teeth), and optimizing the use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers may be more effective than one specific intervention. Table 14 below summarizes some of the strategies that can be used to support and improve adherence to ARV medications. The Centers for Disease Control and Prevention (CDC) offers a web-based toolkit (consisting of four evidence-based HIV medication adherence strategies) to HIV care providers.[27] A recent analysis using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–Adolescent model of HIV disease and treatment modeled the impact of a 12-month hypothetical adherence intervention (based on an interactive smartphone-based reminder system) among youth with HIV in the United States. Compared with the standard of care, the analysis showed that youth-targeted adherence interventions, even with modest efficacy to improve virologic suppression, could improve life expectancy, prevent onward HIV transmissions, and be cost-effective.[28]

Regimen-Related Strategies

To the extent possible, ARV regimens should be simplified with respect to the number of pills or volume of liquid prescribed as well as the number of daily doses, and drugs in the regimen should be chosen to minimize drug interactions and AEs.[29] Efforts should be made to reduce the pill burden and pill size and to prescribe once-daily ARV regimens and single-tablet regimens whenever feasible (see Table 16 in Management of Children Receiving Antiretroviral Therapy). With the introduction of new ARV drug classes and a wider array of once-daily formulations—including some medications that are now available in a small pill size—more options for less toxic, simplified regimens are now available, particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-daily ARV regimens than with twice-daily regimens, and better adherence with single-tablet formulations than with multiple-tablet regimens.[14,30-33] Appendix A, Table 1 shows which ARV drugs are available in fixed-dose combination (FDC) tablets, and Appendix A, Table 2 provides information about minimum body weight requirements and other considerations when using FDC tablets in children.

When nonadherence is related to the poor palatability of a liquid formulation or crushed pills, the offending taste can sometimes be masked with a small amount of flavoring syrup or food if simultaneous administration of food is not contraindicated (see Appendix A: Pediatric Antiretroviral Drug Information).[34] Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children and youth aged 4 years to 21 years found that training children to swallow pills was associated with improved adherence at 6 months post-training.[35] Finally, if drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs by changing the particular drug (or, if necessary, the drug regimen) when feasible.

Patient/Family-Related Strategies

Patient and caregiver education is an essential component of establishing good medication adherence in children. Educating families about adherence should begin before initiating or changing ARV medications and should include a discussion of the goals of therapy, the importance of optimizing adherence, and the specific plans for supporting and maintaining a child's medication adherence.

Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pill boxes. Additionally, it may be helpful to assess the medication adherence of the caregiver or other household members who currently take ARV drugs or other chronic medications.

Several behavioral tools can be used to integrate taking medications into a child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives (including financial incentives) for taking medications, can be effective tools to promote adherence.[36] Treating mental health disorders (e.g., depression) may facilitate adherence to complex ARV regimens.[37,38]

If the child has not been informed of their HIV status, HIV disclosure should be discussed with the caregivers. In a recent review that explored the relationship between ART adherence and disclosure, five studies linked disclosure to improved adherence, four studies found that disclosure led to worse adherence among study participants, and five studies found no association.[39] In interviews with caregivers of children with HIV in South Africa, investigators found that caregivers who had disclosed to their child that they (i.e., the child) were living with HIV were truthful in their communications and named the disease as HIV, but communication about HIV was infrequent and focused on pill taking. By comparison, those who had not disclosed used deception, deflection, and coercion in response to health-related questions and to enforce adherence.[17] The decision to disclose HIV status should not necessarily be expected to improve adherence but should be based on a comprehensive assessment of the psychosocial milieu and the needs of the child and family.

In poorly adherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications, the use of a gastrostomy tube may be considered.[40] If adequate resources are available, home-nursing interventions or DOT also may be beneficial. The evidence is mixed as to the efficacy of programs that are designed to improve adherence through DOT, but DOT may still be a useful strategy for some patients.[41-43] Among 50 adolescents on atazanavir-based second-line therapy participating in a study of modified directly administered ART (mDAART), there was a significant increase in self-reported adherence (relative risk [RR] = 0.1; 95% confidence interval [CI], 0.02–0.8; $P = 0.023$) but a nonsignificant increase in virological suppression to <1,000 copies/mL ($P = 0.105$) among those randomized to the intervention arm compared to the standard of care arm.[44] A recent randomized controlled trial (RCT) of a 12-week multicomponent intervention—including remote coaching, electronic dose monitoring, and tailored outreach (Triggered Escalating Real-Time Adherence)—for viremic youth in the United States demonstrated improved adherence but not viral suppression compared with the standard of care.[21]

Other strategies to support adherence include using mobile applications (apps) that remind patients to take medications; setting patients' cellphone alarms to go off at medication times; sending text-message reminders; conducting motivational interviews; providing pill boxes, blister packaging, and other adherence support tools; and delivering medications to the home. The CDC has an adherence toolbox, which includes a free mobile app (Every Dose Every Day mobile app) that is available through its website.

Several systematic reviews evaluating the use of mobile phone technologies to improve ART adherence (mHealth) have been published. In a recent review, the authors found what they described as "ambiguous results with high variability" about the effectiveness of mHealth interventions to improve adherence in low- and middle-income countries.[45] Of 17 studies, 56% reported a statistically significant positive impact of mHealth on adherence; 44% reported insignificant results. Another systematic review reported that the efficacy of mobile short message service (SMS) interventions varied depending on the specific SMS intervention tested.[46] A third systematic review of the effectiveness of using mobile phone interventions to improve adherence to ART also reported mixed results; effectiveness varied depending on the measured outcomes and the specific intervention (e.g., whether the study evaluated the use of texts or the use of phone calls).[47] It should be noted, however, that the evidence base for effective adherence interventions in adolescents and young adults who are taking daily ART is limited.[48-54]

Lowenthal et al. examined the association between medication-specific reactance—an aversive response to perceived threats against personal agency (behavioral freedom)—and treatment failure in a cohort of adolescents with HIV in Botswana. The authors explain that reactant individuals may hear health messaging as a threat to their perceived freedom and respond by engaging in the opposed behavior. In the study, adolescents were asked to rate the following two questions on a 5-point scale, ranging from definitively false (1) to definitively true (5): (1) whether verbal reminders to take medicines made them want to avoid taking them, and (2) whether they felt anger when reminded to take medicines. Reactant adolescents, those scoring >4, had a 2.05-fold (95% CI, 1.23–3.41) greater odds of treatment failure than non-reactant youth ($P = 0.043$). Psychological reactance needs further study and may provide some insight into adherence behaviors among youth; it also may be important to consider in adherence counseling and in designing interventions.[55]

Two recently published studies provided evidence of the efficacy of peer-based interventions to improve ART adherence and viral suppression among adolescents and young people living with HIV in Africa. In Project YES! in Ndola, Zambia, 273 youth aged 15 to 24 years receiving HIV care in four health facilities—including a children's hospital—were randomly assigned to monthly meetings with youth peer mentors. At 6 months, viral suppression improved in both study arms, but among participants in care at the pediatric clinic, the rate of viral suppression increased from 37.5% to 70.5% in the intervention arm versus the comparison arm, 60.3% to 59.4% (interaction term odds ratio [OR], 4.66; 95% CI, 1.84–11.78).[56] Mavhu et al. tested the efficacy of a peer-led differentiated service delivery intervention on HIV clinical outcomes among adolescents with HIV aged 13 to 19 years in rural Zimbabwe. Sixteen clinics were randomized to standard of care or the enhanced intervention in which adolescents were assigned a community adolescent treatment supporter; attended monthly support group; and received text messages, calls, home visits, and clinic-based counseling. Overall, 212 adolescents were recruited at intervention sites and 284 at control sites, with a median age of 15 years. At 96 weeks, among 479 adolescents with data, 52 (25%) adolescents in the intervention arm versus 97 (36%) in the control arm had viral load >1,000 copies/mL or had died (adjusted prevalence ratio 0.58; 95% CI, 0.36–0.94; $P = 0.03$). The study reported 28 deaths (17 in the intervention arm, 11 in the control arm) and 57 hospital admissions (20 in the intervention arm, 37 in the control arm). These studies demonstrate that peer-based interventions have the potential to improve adherence and health outcomes among youth with HIV.[57]

Further evidence of the efficacy of peer-support interventions for people living with HIV comes from a recent systematic review and meta-analysis, including 20 RCTs comprising 7,605 participants from nine countries. The authors found superior retention in care (RR 1.07; 95% CI, 1.02–1.12 at 12 months follow-up) and better ART adherence (RR 1.06; 95% CI, 1.01–1.10 at 3 months follow-up) but no statistically significant difference in viral suppression (RR = 1.02; 95% CI, 0.94–1.11 at 6 months follow-up) among peer-support participants.[58]

Health Care Provider–Related Strategies

To improve and support ART adherence, providers should maintain a nonjudgmental attitude, establish trust with patients and caregivers, and identify mutually acceptable goals for care. Providers can improve adherence through their relationships with patients' families. This process begins early in a provider's relationship with a family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important. Focus groups and semi-structured interviews were conducted with adolescents and their caregivers participating in a longitudinal adherence study. Participants who self-reported high adherence but for whom electronically monitored data reflected low adherence were selected. Adolescents described hiding and discarding pills and lying about their adherence. Adolescents and parents considered negative feedback for prior poor adherence as motivation for efforts to hide current poor adherence. The authors suggest that positive feedback for truth-telling may help develop family and staff alliances in support of adherence.[59]

Provider characteristics that have been associated with improved patient adherence in adults include consistency, willingness to give information and ask questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child-centered and includes caregivers in adherence support also has been shown to improve treatment outcomes. Immigrant children and families may face unique social and cultural issues; it is important to recognize these issues and facilitate linkage to community resources, particularly for families who are recent immigrants. Providing comprehensive multidisciplinary care (e.g., with nurses, case managers, pharmacists, social workers, psychiatric care providers) also may better serve more complex patient and family needs, including adherence. Provider-initiated education about viral load and counseling targeted at understanding viral load results, the health benefits of undetectable viral load, and the undetectable = untransmittable (U = U) concept are other strategies providers can use.

Table 13. Approaches for Monitoring Medication Adherence

Routine Assessment of Medication Adherence in Clinical Care[a]	Description
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications.[a]
Assess a quantitative self-report of missed doses.	Ask the patient and/or caregiver about the number of missed doses over a defined period (1, 3, or 7 days).
Request a description of the medication regimen.	Ask the patient and/or caregiver about the name, appearance, and number of medications and how often the medications are taken.
Assess barriers to medication administration.	Engage the patient and caregiver in a dialogue about potential barriers to adherence and strategies to overcome them.
Monitor pharmacy refills.	Approaches include a pharmacy-based or clinic-based assessment of on-time medication refills.
Employ telemedicine to monitor and support medication administration.	Telemedicine visits allow remote and often face-to-face contact and provide new opportunities to support families; to visualize ART preparation, handling, and swallowing; and to conduct DOT in the home setting.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to the clinic, conducting home visits, or providing referral to community health nursing.
Targeted Approaches to Monitoring Adherence in Special Circumstances	**Description**
Implement DOT in person and via telemedicine.	Include a brief period of hospitalization if indicated.
Measure drug concentration in plasma or DBS.	Measuring drug concentrations can be considered for particular drugs.
Approaches to Monitoring Medication Adherence in Research Settings	**Description**
Measure drug concentrations in hair.	Measuring hair drug concentrations can be considered for particular drugs; it provides a good measure of adherence over time.[23,60,61]
Use electronic monitoring devices.	Approaches include MEMS caps and Wisepill.
Use mobile phone-based technologies.	Approaches include interactive voice response, text messaging, and mobile apps.

[a] See Clinical and Laboratory Monitoring of Pediatric HIV Infection regarding the frequency of adherence assessment after initiating or changing therapy.

Key: apps = applications; ART = antiretroviral therapy; DBS = dried blood spots; DOT = directly observed therapy; MEMS = Medication Event Monitoring System

Table 14. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on the need for treatment and adherence. • Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or the caregiver that may affect adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible. • Determine whether the child is aware of their HIV status. Consider talking to the child's caregivers about disclosing this information to the child in a developmentally appropriate way. • Identify family, friends, health team members, and others who can support adherence. • Educate the patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and the potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed. • Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them in arranging administration during day care, school, and in other settings, when needed. Consider home delivery of medications. • Establish a patient's readiness to take medication by staging practice sessions or by other means. • Schedule a home visit or telemedicine visit to review medications and determine how they will be administered in the home setting. • In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess the tolerability of the chosen medications.
Medication Strategies
• Choose the simplest regimen possible; reduce dosing frequency, pill size, and number of pills (see Appendix A, Table 1 and Appendix A, Table 2). • When choosing a regimen, consider the patient's daily and weekly routines and potential variations in patient and family activities. • Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability). • Choose drugs with the fewest AEs; provide anticipatory guidance for managing AEs. • Simplify food requirements for medication administration. • Prescribe drugs carefully to avoid adverse drug–drug interactions. • Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.
Follow-Up Intervention Strategies
• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed. • Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens. • Provide education and counseling that explain the meaning and significance of viral load results. • Use patient education aids, including pictures, calendars, and stickers. • Encourage the use of pill boxes, reminders, mobile apps, alarms, and timers. • Provide follow-up clinic visits, telephone calls, text messages, and telemedicine visits to support and assess adherence.

- Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that decrease adherence.
- Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.
- Consider DOT at home, in the clinic, or, in certain circumstances, during a brief period of inpatient hospitalization.
- Consider gastrostomy tube use in certain circumstances.
- Information on other interventions to consider can be found at the Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions on the CDC's website.
- Consult the CDC Every Dose Every Day toolkit.

Key: apps = applications; AE = adverse effect; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy

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Management of Medication Toxicity or Intolerance

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• In children with HIV who have severe or life-threatening toxicity (e.g., a hypersensitivity reaction), all antiretroviral (ARV) drugs should be stopped immediately **(AIII).** Once symptoms of toxicity have resolved, ARV therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) **(AII*).** • When modifying ARV therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and adverse effect profile should be chosen **(AI*).** • The toxicity and the medication presumed responsible should be documented in the medical record of the patient, and the caregiver and patient should be advised of the drug-related toxicity **(AIII).** • In general, dose reduction is not a recommended option for management of ARV toxicity **(AII*).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents but not studies limited to post-pubertal adolescents*

Medication Toxicity or Intolerance

The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects (AEs) of some antiretroviral (ARV) drugs. AEs have been reported, however, with the use of all ARV drugs. Currently recommended ARV regimens are associated with fewer serious and intolerable AEs than regimens used in the past. In the mid-1990s when combination ART was introduced, AEs were among the most common reasons for switching or discontinuing therapy and for medication nonadherence[1-3] (see Adverse Effects of Antiretroviral Agents in the Adult and Adolescent Antiretroviral Guidelines). In recent clinical trials, however, <10% of ARV-treated patients had treatment-limiting AEs.[4-13]

The incidence of some longer-term complications of ART (e.g., bone or renal toxicity, dyslipidemia, accelerated cardiovascular disease) might be underestimated, because most clinical trials enroll a select group of patients based on highly specific inclusion criteria and the duration of participant follow-up is relatively short.[6,7,14-16] To achieve sustained viral suppression during a child's lifetime, both short- and long-term ART toxicities must be anticipated. The clinician must consider potential AEs and issues with medication palatability when selecting an ARV regimen, as well as the individual child's comorbidities, concomitant medications, and history of drug intolerance or viral resistance.

The AEs caused by ARV drugs can vary from mild, more common symptoms (e.g., gastrointestinal intolerance, fatigue) to infrequent but severe and life-threatening, illness. Drug-related toxicity can be acute (i.e., occurring soon after a drug has been administered), subacute (i.e., occurring within 1 day to 2 days after administration), or late (i.e., occurring after prolonged drug administration). For a few ARV medications, pharmacogenetic markers associated with the risk of early toxicity have been identified; however, the only marker that is routinely screened for is HLA-B*5701, a marker for abacavir (ABC) hypersensitivity.[17] For selected children aged <3 years who require treatment with efavirenz (EFV), an additional pharmacogenetic marker, cytochrome P450 (CYP) 2B6 genotype, should be assessed in an attempt to prevent toxicity[17-21] (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information). For agents such as EFV, therapeutic ranges for plasma concentrations, as determined by therapeutic drug monitoring (TDM), may indicate the need for dose reduction or modification of ART in patients who experience central nervous system (CNS) AEs.

The most common acute and chronic AEs that are associated with currently recommended ARV drugs or drug classes are presented in Tables 15a–15k, which are listed below. These tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies. The tables also include selected references that provide further information about these toxicities in pediatric patients.

- Table 15a. Central Nervous System Toxicity
- Table 15b. Dyslipidemia
- Table 15c. Gastrointestinal Effects
- Table 15d. Hematologic Effects
- Table 15e. Hepatic Events
- Table 15f. Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus
- Table 15g. Lactic Acidosis
- Table 15h. Lipodystrophies and Weight Gain
- Table 15i. Nephrotoxic Effects
- Table 15j. Osteopenia and Osteoporosis
- Table 15k. Rash and Hypersensitivity Reactions

Information on toxicities associated with older ARV drugs that are no longer recommended can be found in the Archived Drugs section and archived toxicity tables.

Management

ART-associated AEs can range from acute and potentially life threatening to chronic and insidious. Serious life-threatening events (e.g., hypersensitivity reaction [HSR] due to ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life threatening (e.g., urolithiasis caused by atazanavir, renal tubulopathy caused by tenofovir disoproxil fumarate) usually can be managed by substituting another ARV agent for the presumed causative agent without interrupting ART. Other chronic, non–life-threatening AEs (e.g., dyslipidemia) can be addressed either by switching the potentially causative agent for another agent or by managing the AE with additional pharmacological or nonpharmacological interventions, such as lifestyle modification.

Management strategies must be individualized for each child, taking into account the severity of the toxicity, the child's viral suppression status, and the available ARV options. Clinicians should anticipate the appearance of common, self-limited AEs and reassure patients that many AEs will resolve after the first few weeks of ART. For example, when initiating therapy with boosted protease inhibitors (PIs), many patients experience gastrointestinal AEs, such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these AEs. Some patients may require antiemetic and antidiarrheal agents for symptom management. CNS AEs are encountered commonly when initiating therapy with EFV. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take EFV-containing regimens at bedtime and on an empty stomach to help minimize these AEs. Patients should be advised that these AEs usually diminish within 2 to 4 weeks of initiating therapy in most people; however, they may persist for months in some patients and may require a medication change.[22] In addition, mild rash can be ameliorated with drugs, such as antihistamines. Addressing AEs is essential, because continued use of an ARV agent that a patient finds intolerable may lead the patient to stop their treatment, risking viral rebound and the development of drug resistance.

In patients who experience intolerable AEs from ART, every attempt should be made to identify the offending agent and to replace the drug with another effective agent as soon as possible.[9,23] For mild-to-moderate toxicities, changing to a drug with a different toxicity profile might be sufficient, and discontinuation of all therapy might not be required. When interrupting a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, many experts will stop the NNRTI for 7 to 14 days before stopping the dual nucleoside analogue reverse transcriptase backbone, because of the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see Table 15k. Rash and Hypersensitivity Reactions) should stop all components of the drug regimen simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the AE has been determined, planning can begin for—

- Resuming therapy with a new ARV regimen that does not contain the offending drug, *or*
- Resuming therapy with the original regimen if the event is attributable to another cause.

All drugs in the ARV regimen should then be started simultaneously, rather than one at a time, while observing the patient for AEs.

When therapy is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and AE profiles should be chosen, when possible.[24-27] Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is permissible only for patients whose viral loads are undetectable.

In general, dose reduction is not a recommended strategy for toxicity management, because inadequate ARV drug levels may lead to decreased virologic efficacy. TDM is not routinely recommended; however, it may be used in the management of a child with mild or moderate toxicity, if the toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range.[28,29] An expert in the management of pediatric HIV should be consulted when considering dose reduction based on the results of TDM. Dose reduction after TDM has been studied most extensively with EFV, because increased CNS toxicity has clearly been associated with higher levels of EFV (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

To summarize, management strategies for drug intolerance include the following:

- Symptomatic treatment of mild-to-moderate, transient AEs.
- Switching one drug for another drug that is active against a patient's virus (e.g., changing to ABC for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor for EFV-related CNS

symptoms) (see Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy).

- Using dose reduction, guided by TDM, after consulting with an expert in pediatric HIV.

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Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution which contains both ethanol (42.4% v/v) and propylene glycol (15.3% w/v) as excipients	**Onset:** • 1–6 days after starting LPV/r **Presentation** *Neonates/Premature Infants:* • Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)	Unknown; rare case reports have been published.	Prematurity Low birth weight Aged <14 days (whether birth was premature or term)	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days unless no other alternatives are available. See Lopinavir/Ritonavir.	Discontinue LPV/r; symptoms should resolve in 1–5 days. If needed, reintroduction of LPV/r can be considered when the patient is outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	**Onset:** • For many symptoms, onset is 1–2 days after starting EFV. • Many symptoms subside or diminish by 2–4 weeks, but symptoms may persist in a significant proportion of patients. **Presentation (May Include One or More of the Following)** *Neuropsychiatric Symptoms:* • Abnormal dreams	Variable, depending on age, symptoms, and assessment method **Children:** • 24% of patients experienced any EFV-related CNS manifestation in one case series, with 18% of participants requiring drug discontinuation. • Five of 45 participants (11%) experienced new-onset seizures in one study of children aged <36	Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL). CYP2B6 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 T/T genotype or co-carriage of CYP2B6	Avoid use of EFV for initial ARV treatment in children and adolescents to prevent EFV-associated CNS side effects. See What to Start: Regimens Recommended for Initial Therapy of Antiretroviral -Naïve Children In situations where EFV treatment may be indicated,	If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration is >4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if a suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with input from an expert pharmacologist).

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• Psychosis • Suicidal ideation or attempted/ completed suicide *Other CNS Manifestations:* • Dizziness • Somnolence • Insomnia or poor sleep quality • Impaired concentration • Seizures (including absence seizures) • Cerebellar dysfunction (e.g., tremor, dysmetria, ataxia) **Note:** CNS side effects (e.g., impaired concentration, abnormal dreams, sleep disturbances) may be more difficult to assess in children.	months; two of these participants had alternative causes for seizures. • Cases of cerebellar dysfunction have been reported in children with very high EFV plasma levels. **Adults:** • 30% incidence for any CNS manifestations of any severity. • 6% incidence for EFV-related, severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality. • One case series reported 20 women with ataxia that resolved upon EFV discontinuation, but frequency was not reported.	516 G/T and 983 T/C variants) History of psychiatric illness or use of psychoactive drugs	consider the following: • Administer EFV on an empty stomach, preferably at bedtime. • Prescreen for psychiatric illness; avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs. • Consider using TDM in children with mild or moderate EFV-associated toxicities.	
	RPV	**Onset:** • Most symptoms occur in the first 4–8 weeks of treatment.	**Adults:** • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (most were	History of neuropsychiatric illness	• Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares *Other CNS Manifestations:* • Headache • Dizziness • Insomnia • Somnolence	Grade 1). Depressive disorders of all severity grades were reported in 9% of patients; 1% of patients discontinued RPV because of severe depressive disorders. Higher frequency of depression and dizziness reported when coadministered with DTG. **Children:** • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt. • Somnolence was reported in 5 of 36 children (14%).			
	RAL	**Onset:** • As early as 3–4 days after starting RAL **Presentation:** • Increased psychomotor activity • Headaches • Insomnia • Depression	**Children:** • Increased psychomotor activity was reported in one child. **Adults:** • Headache • Insomnia (<5% in adult trials)	Elevated RAL concentrations Co-treatment with TDF, a PPI, or inhibitors of UGT1A1 Prior history of insomnia or depression	Prescreen for psychiatric symptoms. Monitor carefully for CNS symptoms. Use with caution in the presence of drugs that increase RAL concentration.	Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms.

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)	• Rare case reports of cerebellar dysfunction in adults			
	DTG	**Onset:** • 7–30 days after starting DTG **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Self-harm thoughts, suicidal ideation or attempted/ completed suicide • Drowsiness • Neurocognitive deficits (lower total competence and school performance) *Other CNS Manifestations (Generally Mild):* • Sleep disturbances • Dizziness • Headache	**Children:** • In a retrospective cohort analysis, neuropsychiatric events that resulted in discontinuation occurred in 2 of 29 (6.8%) children who initiated DTG. • Significantly higher frequency of self-harm or suicidal thoughts reported in children in the ODYSSEY trial receiving DTG (23%) compared to SOC ARVs (5%). They were transient, self-resolved, and did not lead to treatment changes **Adults:** • 2.7% of the neuropsychiatric AEs reported in a large prospective cohort resulted in treatment discontinuation. • Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.	Preexisting depression or other psychiatric illness History of ARV-related neuropsychiatric symptoms Higher frequency of overall neuropsychiatric symptoms reported when DTG is coadministered with ABC; and of depression and dizziness when DTG is coadministered with RPV. However, evidence is conflicting for ABC association.	Use with caution in the presence of psychiatric illness, especially in patients with depression or a history of ARV-related neuropsychiatric symptoms. Consider morning dosing of DTG.	For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists. For mild symptoms, continue DTG and counsel patient that symptoms likely will resolve with time.
	BIC	**Onset:** • 1–63 days after starting BIC (as late as 233 days	**Children:** • One child (1%) had Grade 2 insomnia and anxiety that	Preexisting depression or other	Use with caution in the presence of psychiatric conditions	For persistent or severe neuropsychiatric symptoms, consider

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		for schizoaffective disorders) **Presentation** *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Suicidal ideation or attempted suicide • Schizoaffective disorders • Anxiety *Other CNS Manifestations (Generally Mild):* • Sleep disturbances • Dizziness • Insomnia	led to drug discontinuation in clinical trials. **Adults:** • Overall, the frequency of neuropsychiatric events in BIC and DTG comparator arms appeared similar in adult clinical trials. • Abnormal dreams, dizziness, and insomnia occurred in 1% to 5% of adults. • Suicidal ideation, suicide attempts, schizoaffective disorders, and depression occurred in <1% of adults. • A recent study reported a 3.3% short term BIC-related discontinuation rate due to neuropsychiatric AEs after ART switch in a large cohort of adults living with HIV in routine clinical practice setting.	psychiatric conditions History of ARV-related neuropsychiatric symptoms	or in patients with a history of ARV-related neuropsychiatric symptoms.	discontinuing BIC if a suitable alternative exists. For mild symptoms, continue BIC and counsel patient that symptoms likely will resolve with time.

Key: ABC = abacavir; AE = adverse event; ARV = antiretroviral; BIC = bictegravir; CNS = central nervous system; CYP2B6 = cytochrome P450 2B6; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; SOC = standard of care; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; UGT1A = uridine diphosphate(UDP)-glucuronosyltransferase Family 1 Member A Complex; % v = volume; w = weight

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Table 15b. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Dyslipidemia

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia	**PIs** • All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV, with or without RTV **NRTIs** • Lower incidence reported with TDF than with TAF **NNRTIs** • Lower incidence reported with NVP, RPV, and ETR than with EFV **INSTIs** EVG/c	**Onset** • As early as 2 weeks to months after beginning therapy **Presentation** *PIs* • ↑ LDL-C, TC, and TG *NRTIs* • ↑ LDL-C, TC, and TG. Significant increase in plasma lipid values was observed in adults switching from TDF to TAF, regardless of third agent or presence of a boosting agent.	Reported frequency varies with specific ARV regimen, duration of ART, and the specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% of young children receiving LPV/r will have lipid abnormalities. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Pooled dyslipidemia prevalence of 39.5% and an incidence of 32% (191 per 1,000 person-years)	Advanced-stage HIV disease High-fat, high-cholesterol diet Sedentary lifestyle Obesity Hypertension Smoking Family history of dyslipidemia or premature ASCVD Metabolic syndrome Fat maldistribution	**Prevention** • Low-fat diet • Exercise • Smoking-prevention counseling • Use of ARVs associated with a lower prevalence of dyslipidemia, such as INSTIs and, to a lesser extent, newer PIs (e.g., ATV, DRV). • When considering a TDF-based or a TAF-based regimen, the lipid-lowering beneficial effect of TDF should be weighed against its potential for increased renal and bone toxicities. **Monitoring**[a] *Adolescents and Adults* • Obtain FLP (TC, HDL-C, non-HDL-C, LDL-C, and TG) twice (>2 weeks but ≤3 months apart, average these results). Monitor FLP every 6 months (for	Assess all patients for additional ASCVD risk factors. Patients with HIV are considered to be at moderate risk of ASCVD.[b] ARV regimen changes should be considered, especially when the patient is receiving older PIs (e.g., LPV/r) and/or RTV boosting. Switching to a PI-sparing regimen, a PI-based regimen with a more favorable lipid profile or COBI boosting causes a decline in LDL-C or TG values. However, the lipid-lowering effect for LDL-C is less pronounced than with statin therapy. Refer patients to a lipid specialist early if LDL-C is ≥250 mg/dL or TG is ≥500 mg/dL. If LDL-C is ≥130 mg/dL but <250 mg or TG is ≥150 mg/dL but <500 mg/dL, the following staged treatment approach is recommended by the NHLBI guidelines:[b] • Implement diet, nutrition, and lifestyle management for 6–9 months. Consult with a dietician if one is available.

		NNRTIs • ↑ LDL-C, TC, and HDL-C	reported in a recent meta-analysis and a recent review of a large consortium of prospective observational cohorts, respectively.		abnormal results) or every 12 months (for normal results). *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors* • Obtain nonfasting screening lipid profiles at entry into care and then every 6–12 months, depending on the results. • If TG or LDL-C is elevated or if a patient has additional risk factors, obtain FLP. *Children with Lipid Abnormalities and/or Additional Risk Factors* • Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates* • Obtain 12-hour FLP, LFT, and CK at 4 weeks, 8 weeks, and 3 months after starting lipid therapy. • If minimal alterations in AST, ALT, and CK are indicated, monitor every 3–4 months during the first year and	• If a 6- to 9-month trial of lifestyle modification fails and the patient is aged ≥10 years, consider implementing lipid-lowering therapy after consulting a lipid specialist. • Statin therapy should be considered for patients with elevated LDL-C levels. NHLBI provides recommendations for statin therapy in patients with specific LDL-C levels and risk factors.[b] Concurrent substitution—preferably to ARVs with no inhibitory or inducing effect on CYP3A4 or OATP1B1 (e.g., INSTI)—also should be considered as appropriate to limit drug–drug interaction potential. • Drug therapy can be considered in cases of severe hypertriglyceridemia (TG ≥500 mg/dL). Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used. The long-term risks of lipid abnormalities in children who are receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature ASCVD.

					every 6 months thereafter (or as clinically indicated). • Repeat FLP 4 weeks after increasing doses of antihyperlipidemic agents.	

[a] Because of the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and TG from nonfasting blood samples and follow-up abnormal values with a test done in the fasted state.

[b] Refer to the NHLBI guidelines: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (PDF).

Key: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; CYP3A4 = cytochrome P450 3A4; DRV = darunavir; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FLP = fasting lipid profile; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OATP1B1 = organic anion transporter polypeptide 1B1; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides

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Table 15c. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Nausea/ Vomiting	All ARV drugs, but most notably RTV-boosted PIs	**Onset** • Early **Presentation** • Nausea and emesis, both of which may be associated with anorexia and/or abdominal pain	Varies by ARV agent; generally <15%	Unknown	• Instruct patient to take PIs with food. • Monitor for weight loss and ARV adherence.	• Reassure the patient that these adverse effects generally improve over time (usually in 6–8 weeks). • Consider switching to ARV drugs with smaller tablet sizes (see Appendix A,Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents). • Provide supportive care. • In extreme or persistent cases, use antiemetics or switch to another ARV regimen.
Diarrhea	All ARV drugs, but most notably RTV-boosted PIs	**Onset** • Early **Presentation** • More frequent bowel movements and stools that are generally soft	Varies by ARV agent; generally <15%	Unknown	Monitor for weight loss and dehydration.	• In prolonged or severe cases, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea. • Reassure patient that this adverse effect generally improves over time (usually in 6–8 weeks). Consider switching to another ARV

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
						regimen in persistent and severe cases. • Treatment data in children are lacking; however, the following strategies may be useful when the ARV regimen cannot be changed: • Modifying the diet • Using bulk-forming agents (e.g., psyllium) • Using antimotility agents (e.g., loperamide) • Using crofelemer, which is approved by the FDA to treat ART-associated diarrhea in adults aged ≥18 years; no pediatric data are available.
Pancreatitis	Rare, but may occur with NRTIs or RTV-boosted PIs	**Onset** • Any time, usually after months of therapy **Presentation** • Emesis, abdominal pain, elevated amylase and lipase levels (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)	<2%	Use of concomitant medications that are associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin) Hypertriglyceridemia Advanced HIV infection Previous episode of pancreatitis Alcohol use	Measure serum amylase and lipase concentrations if persistent abdominal pain develops.	• Discontinue offending agent and **avoid reintroduction.** • Manage symptoms of acute episodes. • If pancreatitis is associated with hypertriglyceridemia, consider using interventions to lower TG levels.

Key: ART = antiretroviral therapy; ARV = antiretroviral; FDA = U.S. Food and Drug Administration; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole

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Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia[a]	ZDV	**Onset** • Variable; weeks to months after starting therapy **Presentation** *More Common* • Asymptomatic • Mild fatigue • Pallor • Tachypnea *Rare* • Congestive heart failure	**Newborns Exposed to HIV** • Severe anemia is uncommon but might be coincident with physiologic Hgb nadir. **Children with HIV Who Are Taking ARV Drugs** • Anemia is two to three times more common with ZDV-containing regimens than with all other regimens.	**Newborns Exposed to HIV** • Premature birth is the most common risk factor. • *In utero* exposure to ZDV-containing regimens • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis or presumptive HIV therapy, particularly ZDV plus 3TC and NVP **Children with HIV Who Are Taking ARV Drugs** • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency)	**Newborns Exposed to HIV** • Obtain CBC at birth. • Consider repeating CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or who are known to have low birth Hgb) and for neonates who receive ZDV beyond 4 weeks. **Children with HIV Who Are Taking ARV Drugs** • Avoid using ZDV in children with severe anemia when alternative agents are available. • Obtain CBC as part of routine care (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).	**Newborns Exposed to HIV** • Anemia rarely requires intervention unless it is symptomatic or Hgb <7.0 g/dL. • ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). **Children with HIV Who Are Taking ARV Drugs** • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting iron deficiency, OIs, and malignancies. • For persistent, severe anemia that is thought to be associated with

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
				• Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • OIs of the bone marrow • Malnutrition		ARV drugs (typically macrocytic anemia), switch to a regimen that does not contain ZDV.
Macrocytosis	ZDV	**Onset** • Within days or weeks of starting therapy **Presentation** • Asymptomatic, but MCV often is >100 fL • Sometimes associated with anemia	>90% to 95% for all ages	None	No monitoring required—macrocytosis can be detected if CBC is obtained as part of routine care (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).	No management required.
Neutropenia[a]	ZDV	**Onset** • Variable **Presentation** • Asymptomatic	**Newborns Exposed to HIV** • Rare **Children with HIV Who Are Taking ARV Drugs** • 2% to 4% of children on ARV drugs • Highest rates occur in children on ZDV-	**Newborns Exposed to HIV** • *In utero* exposure to ARV drugs • Combination ARV prophylaxis, particularly ZDV plus 3TC and NVP **Children with HIV Who Are Taking ARV Drugs**	**Children with HIV Who Are Taking ARV Drugs** • Obtain CBC as part of routine care.	**Newborns Exposed to HIV** • No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC reaches <500 cells/mm^3. ZDV administration can be limited to 4 weeks in low-risk neonates (see

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
			containing regimens	• Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)		Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection). **Children with HIV Who Are Taking ARV Drugs** • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • In cases of persistent, severe neutropenia that is thought to be associated with ARV drugs, switch to a regimen that does not contain ZDV.

[a] HIV infection itself, OIs, and medications that are used to prevent OIs (e.g., TMP-SMX) can all contribute to anemia and neutropenia. Prolonged use of NVP with ZDV in three drug regimens for the prevention of perinatal HIV transmission has been associated with increased rates of anemia and neutropenia in some, but not all, studies. The effects are of uncertain clinical significance and appear to be transient.

Key: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; g/dL = grams per deciliter; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; OI = opportunistic infection; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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Table 15e. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Hepatic Events

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatitis	• Most ARV drugs have been associated with hepatitis, but a strong association exists between hepatitis and the use of NVP and EFV. • NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs. • NRTIs, especially ZDV, have been associated with lactic acidosis and hepatic steatosis.	**Onset** • Acute toxic hepatitis occurs most commonly within the first few months of therapy, but it can occur later. • Steatosis presents after months or years of therapy. • Patients with HBV coinfection can experience a hepatitis flare with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. A flare also can occur with the emergence of resistance to 3TC or FTC (especially if the patient is receiving only one anti-HBV agent). Note that TDF and TAF have high barriers to resistance when used to treat HBV. • Hepatitis can be a manifestation of IRIS if it occurs early in	Uncommon	• HBV or HCV coinfection • Underlying liver disease • Use of other hepatotoxic medications and supplements (e.g., St. John's wort [*Hypericum perforatum*], chaparral [*Larrea tridentata*], germander [*Teucrium chamaedrys*]) • Alcohol use • Pregnancy • Obesity • Higher drug concentrations of PIs **For NVP-Associated Hepatic Events in Adults** • Female sex with pre-NVP CD4 count >250 cells/mm³	**Prevention** • Avoid concomitant use of hepatotoxic medications. • In patients with elevated levels of hepatic enzymes (>5 times to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP. **Monitoring** *For ARV Drugs Other than NVP* • Obtain AST and ALT levels at baseline and at least every 3–4 months thereafter;[b] monitor at-risk patients more frequently (e.g., those with HBV or HCV coinfection or elevated baseline	Evaluate the patient for other infectious and noninfectious causes of hepatitis and monitor the patient closely. **Asymptomatic Hepatitis** • Potentially offending ARV drugs should be discontinued if ALT or AST level is >5 times ULN. **Symptomatic Hepatitis** • Discontinue all ARV drugs and other potentially hepatotoxic drugs. • If a patient experiences hepatitis that is attributed to NVP, **NVP should be discontinued permanently.** • Consider viral causes of hepatitis:

		therapy, especially in patients with HBV or HCV coinfection. **Presentation** • Asymptomatic elevation of AST and ALT levels • Symptomatic hepatitis with nausea, fatigue, and jaundice • Hepatitis may present in the context of HSR with rash, lactic acidosis, and hepatic steatosis.		• Male sex with pre-NVP CD4 count >400 cells/mm^3 • Population-specific HLA types[a]	AST and ALT levels). *For NVP* • Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.	HAV, HBV, HCV, EBV, and CMV.
Indirect Hyperbilirubinemia	ATV	**Onset** • Within the first months of therapy **Presentation** • Can be asymptomatic or associated with jaundice. • Levels of direct bilirubin can be normal or slightly elevated when levels of indirect bilirubin are very high. • Normal AST and ALT	In long-term follow-up, 9% of children who were receiving ATV had at least one total bilirubin level >5 times ULN, and 1.4% of children experienced jaundice.	None established	**Monitoring** • No ongoing monitoring needed. • After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels can improve over time.	Isolated indirect hyperbilirubinemia is not an indication to stop ATV. Psychological impact of jaundice should be evaluated, and alternative agents should be considered. Jaundice can result in nonadherence, particularly in adolescents; this side effect should be discussed with patients.

[a] For example, HLA-DRB1*0101 in White people, HLA-DRB1*0102 in South African people, and HLA-B35 in Thai people and White people.

[b] Less frequent monitoring can be considered in children whose clinical status has been stable for >2 years to 3 years (see Clinical and Laboratory Monitoring of Pediatric HIV Infection).

Key: 3TC = lamivudine; ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; DTG = dolutegravir; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; ZDV = zidovudine

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Table 15f. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, and Diabetes Mellitus

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, and Diabetes Mellitus[a]	• ZDV, LPV/r and, possibly, other PIs and INSTIs	**Onset** • Weeks to months after beginning therapy **Presentation** • Asymptomatic fasting hyperglycemia (which sometimes occurs in the setting of lipodystrophy), metabolic syndrome, or growth delay • Symptomatic DM (rare)	**Children** • IR, 6% to 12% (incidence is higher during puberty, 20% to 30%) • IFPG, 0% to 7% • IGT, 3% to 4% • DM, 0.2 per 100 child-years	**Risk Factors for Type 2 DM** • Lipodystrophy • Metabolic syndrome • Family history of DM • High BMI (obesity)	**Prevention** • Lifestyle modification **Monitoring** • Monitor for signs of DM, change in body habitus, and acanthosis nigricans. • Obtain RPG levels at initiation of ART, 3–6 months after ART initiation, and yearly thereafter. • In patients with an RPG ≥140 mg/dL, obtain FPG after an 8-hour fast and consider referring the patient to an endocrinologist.	• Counsel patient on lifestyle modification (e.g., implementing a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increasing physical activity; ceasing smoking). • Recommend that the patient consult with a dietician. • If the patient is receiving ZDV, switch to TAF, TDF, or ABC. **For Patients with Either an RPG ≥200 mg/dL Plus Symptoms of DM or an FPG ≥126 mg/dL** • These patients meet diagnostic criteria for DM; consult an endocrinologist. **For Patients with an FPG of 100–125 mg/dL**

						• Impaired FPG suggests insulin resistance; consult an endocrinologist. **For Patients with an FPG <100 mg/dL** • This FPG is normal, but a normal FPG does not exclude IR. Recheck FPG in 6–12 months.

[a] IR, asymptomatic hyperglycemia, IFPG, IGT, and DM form a spectrum of increasing severity.

IR: Often defined as elevated insulin levels for the level of glucose observed.
IFPG: Often defined as an FPG of 100–125 mg/dL.
IGT: Often defined as an elevated 2-hour plasma glucose (PG) of 140–199 mg/dL in a 75-g oral glucose tolerance test (OGTT) (or, if the patient weighs <43 kg, 1.75 g per kg of glucose up to a maximum of 75 g).
DM: Often defined as either an FPG ≥126 mg/dL, an RPG ≥200 mg/dL in a patient with hyperglycemia symptoms, a glycosylated hemoglobin (HgbA1c) of ≥6.5%, or a 2-hour PG ≥200 mg/dL in an OGTT.

However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend performing routine measurements of insulin levels, HgbA1c, or glucose tolerance without consulting an endocrinologist. These guidelines are instead based on the readily available RPG and FPG levels.

Key: ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; DM = diabetes mellitus; FPG = fasting plasma glucose; IFPG = impaired fasting plasma glucose; IGT = impaired glucose tolerance; INSTI = integrase strand transfer inhibitor; IR = insulin resistance; LPV/r = lopinavir/ritonavir; mg/dL = milligrams per deciliter; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Table 15g. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Lactic Acidosis

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lactic Acidosis	**NRTIs** • ZDV • Less likely with 3TC, FTC, ABC, TAF, and TDF **Other Drugs** • See the Risk Factors and Prevention/ Monitoring columns for information regarding the toxicity of propylene glycol when LPV/r oral solution is used in neonates.	**Onset** • Generally after years of exposure **Presentation** • Lactic acidosis may be clinically asymptomatic. *Lactic Acidosis May Also Present with Insidious Onset of a Combination of Signs and Symptoms* • Generalized fatigue, weakness, and myalgias • Vague abdominal pain, weight loss, unexplained nausea, or vomiting • Dyspnea • Peripheral neuropathy **Note:** Patients may present with acute multiorgan failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure).	3TC, FTC, ABC, TAF, and TDF are less likely to induce clinically significant mitochondrial dysfunction than ZDV.	**Adults** • Female sex • High BMI • Chronic HCV infection • African American race • Coadministration of TDF with metformin • Overdose of propylene glycol • CD4 count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possible pregnancy **Preterm Infants or Any Neonates Who Have Not Attained a Postmenstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days** • Exposure to propylene glycol, which is used as a diluent in LPV/r oral solution, because these newborns have a diminished ability to metabolize propylene	**Prevention** • Due to the presence of propylene glycol as a diluent, LPV/r oral solution **should not be used** in preterm neonates or any neonate who has not attained a postmenstrual age of 42 weeks and a postnatal age of ≥14 days. • Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy. **Monitoring** *Asymptomatic Patients* • Routine measurement of serum lactate **is not recommended.** *Patients with Clinical Signs or Symptoms Consistent with Lactic Acidosis* • Obtain blood lactate level.[a] • Additional diagnostic evaluations should include serum bicarbonate, anion gap, and/or arterial blood gas; amylase and lipase;	**For Patients with Lactate 2.1–5.0 mmol/L (Confirmed with a Second Test)** • Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic work-up. **For Patients with Lactate >5.0 mmol/L (Confirmed with a Second Test)[b] or >10.0 mmol/L (Any One Test)** • Discontinue all ARV drugs. • Provide supportive therapy (e.g., IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues). **Anecdotal (Unproven) Supportive Therapies** • Administer bicarbonate infusions, THAM, high doses of thiamine and riboflavin, and oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C).

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
				glycol may lead to accumulation, increasing the risk of adverse events.	serum albumin; and hepatic transaminases.	Following the resolution of clinical and laboratory abnormalities, resume therapy either with an NRTI-sparing regimen or a revised NRTI-containing regimen. Institute a revised NRTI-containing regimen with caution, using NRTIs that are less likely to induce mitochondrial dysfunction (ABC, TAF, TDF, FTC, or 3TC). Lactate should be monitored monthly for ≥3 months.

[a] Blood for lactate determination should be collected, without prolonged tourniquet application or fist clenching, into a pre-chilled, gray-top, fluoride-oxalate-containing tube and transported on ice to the laboratory to be processed within 4 hours of collection.

[b] Management can be initiated before receiving the results of the confirmatory test.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; ZDV = zidovudine

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Table 15h. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy (Fat Maldistribution) General Information	• See below for specific associations.	**Onset** • Increase in trunk and limb fat is the first sign; peripheral fat wasting may not appear for 12–24 months after ART initiation.	• Frequency is low (<5%) with current regimens.	• Genetic predisposition • Puberty • HIV-associated inflammation • Older age • Longer duration of ART • Body habitus	**Prevention** • Initiate a calorically appropriate low-fat diet and an exercise regimen. **Monitoring** • BMI measurement • Waist circumference and waist-hip ratio	• Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs. • Improvement in fat maldistribution can vary following a regimen change. Improvement may occur after several months or years, or it may not occur at all.
Central Lipohypertrophy or Lipo-Accumulation	• Can occur in the absence of ART, but these conditions most often are associated with the use of PIs and EFV.	**Presentation** • Central fat accumulation with increased abdominal girth, which may include a dorsocervical fat pad (buffalo hump). Gynecomastia may occur in males, or breast hypertrophy may occur in females, particularly with the use of EFV.	• Frequency is low (<5%) with current regimens.	• Obesity before initiation of therapy • Sedentary lifestyle	**Prevention** • Initiate a calorically appropriate low-fat diet and an exercise regimen. **Monitoring** • BMI measurement • Waist circumference and waist-hip ratio measurements	• Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate diet that is low in saturated fats and simple carbohydrates and starting an exercise regimen, especially strength training). • Recommend smoking cessation (if applicable) to decrease future CVD risk.

						• Consider using an INSTI instead of a PI or EFV, although some INSTIs may be associated with generalized weight gain (see below). **Data Are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children** • Recombinant human growth hormone • Growth hormone–releasing hormone • Metformin • Thiazolidinediones • Recombinant human leptin • Anabolic steroids • Liposuction
Facial/Peripheral Lipoatrophy	• Most cases are associated with the use of ZDV, a thymidine analogue NRTI.	**Presentation** • Thinning of subcutaneous fat in the face, buttocks, and extremities, measured as a decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.	• Frequency is low (<5%) with current regimens.	• Underweight before ART initiation	**Prevention** • Limit the use of ZDV. **Monitoring** • Patient self-report and physical examination are the most sensitive methods of monitoring lipoatrophy.	• Replace ZDV with another NRTI when possible. **Data Are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children** • Injections of poly-L-lactic acid • Recombinant human leptin • Autologous fat

						transplantation • Thiazolidinediones
Weight Gain	• Significant weight gain may occur with all ARV regimens, but it appears to be more pronounced with DTG, BIC, and TAF.	**Onset** • Gradual weight gain after initiating ARV drugs is common with all currently used regimens. The mechanism for weight gain is unclear and under investigation.	• Rate of development of obesity is unclear.	**In Infants and Children** • Have not been evaluated yet **In Adolescents** • Female sex • Pre-treatment obesity **In Adults** • Low pre-treatment BMI • Older age • Female sex • Black race	**Prevention** • Initiate a calorically appropriate low-fat diet and an exercise regimen. **Monitoring** • BMI measurement • Waist circumference and waist-hip ratio measurements	• Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate healthy diet that is low in saturated fats and simple carbohydrates and starting an exercise regimen, especially strength training).

Key: ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; BMI = body mass index; CVD = cardiovascular disease; DTG = dolutegravir; DXA = dual energy X-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide; ZDV = zidovudine

See the archived version of Supplement III, February 23, 2009, Pediatric Guidelines on the Clinical info website for a more complete discussion and reference list.

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Table 15i. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Urolithiasis/ Nephrolithiasis	ATV DRV causes crystalluria, but it is not associated with nephrolithiasis.	**Onset** • Weeks to months after starting therapy **Clinical Findings** • Crystalluria • Hematuria • Pyuria • Flank pain • Increased creatinine levels in some cases	ATV-related nephrolithiasis occurs in <10% of patients and has been reported after stopping ATV.	In adults, elevated urine pH (>5.7) The risk factors in children are unknown.	**Prevention** • Maintain adequate hydration. **Monitoring** • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control. Consider using another ARV drug in place of ATV.
Renal Dysfunction	TDF	**Onset** • Variable; in adults, renal dysfunction may occur weeks to months after initiating therapy. • Hypophosphatemia appears at a median of 18 months. • Glucosuria may occur after 1 year of therapy. • Abnormal urine protein/osmolality ratio may	**Adults** • Approximately 2% of adults experience increased serum creatinine levels. • Approximately 0.5% of adults experience severe renal complications. **Children** • Approximately 4% of children experience	**Risk May Increase in Children with the Following Characteristics** • Aged >6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • Hypertension	Monitor urine protein, urine glucose, and serum creatinine at 3- to 6-month intervals. Some Panel members routinely monitor serum phosphate levels in patients who are taking TDF. Measure serum phosphate if the patient experiences persistent proteinuria	If TDF is the likely cause, consider using an alternative ARV drug. TAF has significantly less toxicity than TDF. Changing from TDF to TAF may improve renal function.

		be an early indicator. **Presentation** *More Common* • Increased serum creatinine levels, proteinuria, normoglycemic glucosuria • Increased urinary protein/creatinine ratio and albumin/creatinine ratio • Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain or muscle weakness *Less Common* • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy and advanced HIV infection.	• Diabetes • Concurrent use of PIs (especially LPV/r) and preexisting renal dysfunction • Longer duration of TDF treatment • The presence of the apolipoprotein L1 variants G1 and G2 appears to increase the risk of renal abnormality in children with HIV. These alleles are more common in persons of Black descent.	or glucosuria or has symptoms of bone pain, muscle pain, or weakness. Because toxicity risk increases with the duration of TDF treatment, do not decrease the frequency of monitoring over time.	
Elevation in Serum Creatinine	DTG, COBI, RPV, BIC	**Onset** • Within 1 month of starting treatment **Presentation** • Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in serum creatinine levels without a true change in eGFR.	Common laboratory finding.	The risk factors in children are unknown.	Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or if increases continue over time.	No need to change therapy. Reassure the patient about the benign nature of the laboratory abnormality.

		• Clinicians need to distinguish between a true change in eGFR and other causes. A true change may be associated with other medical conditions, the continuing rise of serum creatinine levels over time, and albuminuria.				

Key: ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; LPV/r = lopinavir/ritonavir; mg/dL = milligrams per deciliter; Panel = The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Table 15j. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Osteopenia and Osteoporosis	Any ARV regimen **Specific Agents of Concern** • TDF, especially when used in a regimen that includes a boosting agent (i.e., RTV, COBI) • PIs (LPV, ATV>DRV) • EFV	**Onset** • Any age; decrease in BMD is usually seen soon after initiating ART. **Presentation** • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., a fracture with minimal trauma).	**BMD *z score* Less Than −2.0** • <10% in U.S. cohorts • Approximately 10% to 20% in international cohorts	• Longer duration and greater severity of HIV disease • Detectable viral load • Vitamin D insufficiency/deficiency • Delayed growth or pubertal delay • Low BMI • Lipodystrophy • Smoking • Prolonged systemic corticosteroid use • Medroxyprogesterone use • Lack of weight-bearing exercise	**Prevention** • Ensure that the patient has sufficient intake and levels of both calcium and vitamin D. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone). • Use TAF instead of TDF whenever possible. • Use TDF with RPV or an unboosted INSTI. • When using TDF or EFV in a regimen, consider measuring vitamin D levels and supplementing with vitamin D3 if deficiency is identified. **Monitoring** • Assess nutritional intake (calcium, vitamin D, and total calories). • Consider measuring serum 25-OH-vitamin D levels, particularly in patients who are taking ARV drugs of concern.[a] • DXA is rarely indicated.[b]	• Same options as for prevention. • Consider changing the ARV regimen (e.g., switching from TDF to TAF, and/or from LPV/r to RPV or an unboosted INSTI whenever possible). • Supplement with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. There is no clear benefit to administering daily supplemental vitamin D3 doses that are >4,000 IU. If patients are receiving a daily dose of vitamin D3 that is >4,000 IU, consider monitoring levels of 25-OH-vitamin D. • An increase in BMD was seen in one trial that evaluated the use of alendronate in youth with HIV and low BMD. However, the role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

[a] Drugs of greatest concern are TDF and EFV. Some experts measure 25-OH-vitamin D in children with HIV with additional risk factors, including living at high latitudes, sun avoidance, low dietary intake, and obesity (U.S. Preventive Services Task Force 2021 guidelines).

[b] DXA scanning is not routinely recommended for children and youth who are being treated with TDF. DXA scanning can be considered for children and youth who are receiving additional medications which also affect bone density or have non-HIV related conditions for which DXA scans may be indicated (such as cerebral palsy).

Key: 25-OH-vitamin D = 25-hydroxy vitamin D; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BMD = bone mineral density; BMI = body mass index; COBI = cobicistat; DRV = darunavir; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; IU = international unit; LPV = lopinavir; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Table 15k. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Rash	• Any ARV drug can cause rash.	**Onset** • First few days to weeks after starting new ARV drug(s) **Presentation** • Most rashes mild to moderate diffuse maculopapular eruptions **Note:** A rash can be the initial manifestation of systemic hypersensitivity (see the SJS/TEN/EM major and HSR sections below).	**Common (>10%)** • EFV • ETR • FTC • NVP **Less Common (5% to 10%)** • ABC • ATV • DRV • TDF **Unusual (2% to 4%)** • BIC • LPV/r • MVC • RAL • RPV	• Sulfonamide allergy is a risk factor for rash in patients who are taking PIs that contain a sulfonamide moiety (i.e., DRV). • Polymorphisms in CYP2B6 and multiple HLA loci are associated with an increased risk of rash in patients who are taking NVP.	**When Starting NVP or Restarting NVP After Interruptions of >14 Days** • Utilize once-daily lead-in dosing.[a] This may not be necessary in children ages <2 years.[b] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess the patient for rash severity, mucosal involvement, and other signs of systemic reaction.	**Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement** • Most rashes will resolve without intervention; ARV drugs can be continued while monitoring.[a] • Antihistamines may provide some relief. **Severe Rash and/or Rash Accompanied by Systemic Symptoms** • Manage as SJS/TEN/EM major, DRESS, or HSR as applicable (see below). **Rash in Patients Receiving NVP** • Given the elevated risk of HSR, measure hepatic transaminases. • If hepatic transaminases are elevated, NVP **should be discontinued and not restarted** (see the HSR section below).
SJS/TEN/EM Major	• Many ARV drugs, especially NNRTIs (see the Estimated Frequency column)	**Onset** • First few days to weeks after starting new ARV drug(s) **Presentation** • Initial rash may be mild, but it often becomes painful,	**Infrequent** • NVP (0.3%) • EFV (0.1%) • ETR (<0.1%) **Case Reports** • ABC	**Adults** • Female sex • Patients who are Black, Asian, or Hispanic at higher risk	**When Starting NVP or Restarting NVP After Interruptions of >14 Days** • Utilize once-daily lead-in dosing.[a] This may not be necessary in children aged <2 years.[b]	• Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). • Provide intensive supportive care, including IV hydration, aggressive wound care, eye care, labial adhesion preventive care, pain management, and antipyretics.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		evolving to blister/bulla formation with necrosis in severe cases. Usually involves mucous membrane ulceration and/or conjunctivitis. • Systemic symptoms may also include fever, tachycardia, malaise, myalgia, and arthralgia.	• ATV • DRV • LPV/r • RAL • ZDV		• Counsel families to report symptoms as soon as they appear.	Parenteral nutrition and antibiotics may also be necessary. • Corticosteroids and/or IVIG are sometimes used, but the use of these interventions is controversial. • **Do not reintroduce** the offending medication. • In cases where a patient experiences SJS/TEN/EM major while taking an NNRTI, many experts would avoid using other NNRTIs when restarting ART.
DRESS	• DRV, DTG, EFV, ETR, NVP, RAL, RPV	**Onset** • 1–8 weeks after starting new ARV drug(s) **Presentation** • Fever • Lymphadenopathy • Facial swelling • Morbilliform to polymorphous rash • Peripheral eosinophilia • Atypical circulating lymphocytes • Internal organ involvement (particularly the liver and/or kidneys)	• Rare	• Unknown • Potential association with HLA-B*53:01 and RAL-induced DRESS	• Obtain a CBC and AST, ALT, and creatinine levels from patients who present with suggestive symptoms.	• Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). • The role of systemic steroids or IVIG in treatment is unclear; consultation with a specialist is recommended. • Provide supportive care for end-organ disease. • **Do not reintroduce** the offending medication.
HSR • With or without skin involvement	ABC	**Onset** *With First Use*	• <1% to 9% (varies by ethnicity)	• HLA-B*5701 (HSR is very uncommon in people who are HLA-B*5701 negative).	• Screen for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is present.** The	• Discontinue all ARV drugs and investigate other causes of the symptoms (e.g., a concurrent viral illness).

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
and excluding SJS/TEN		• Within first 6 weeks of initiating ABC *With Reintroduction* • Within hours of initiating ABC **Presentation** • Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms (e.g., dyspnea). • With continuation of ABC, symptoms may progress to hypotension and vascular collapse. With rechallenge, symptoms can mimic anaphylaxis.		• The risk of HSR is higher in patients who are white than in patients who are Black or East Asian.	medical record should clearly indicate that ABC is **contraindicated** in these patients. • When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	• Provide symptomatic treatment. • Most symptoms resolve within 48 hours after discontinuing ABC. **Do not rechallenge** with ABC even if the patient is HLA-B*5701 negative.
	NVP	**Onset** • Occurs most frequently in the first few weeks of therapy but can occur through 18 weeks. **Presentation** • Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or	• Occurs in 4% of patients on average, with a range of 2.5% to 11%	**Adults** • ARV-naive with a higher CD4 count (>250 cells/mm³ in women; >400 cells/mm³ in men) • Female sex (risk is threefold higher in females than in males). **Children** • NVP hepatotoxicity and HSR are less common in prepubertal children	**When Starting NVP or Restarting NVP After Interruptions of >14 Days** • A 2-week lead-in period with once-daily dosing, followed by dose escalation to twice daily as recommended, may reduce the risk of reaction.[a] This may not be necessary in children aged <2 years.[b] • Counsel families about signs and symptoms of	• Discontinue all ARV drugs. • Consider other causes of hepatitis and discontinue all hepatotoxic medications. • Provide supportive care as indicated, and monitor the patient closely. • **Do not reintroduce NVP.** It is unclear whether it is safe to use other NNRTIs after a patient experiences symptomatic hepatitis due to NVP, and many experts

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		without skin rash that may progress to hepatic failure with encephalopathy		than in adults, and both are uncommon in infants. • High CD4 percentage is associated with an increased risk of NVP toxicity. In the PREDICT Study, the risk of NVP toxicity (rash, hepatotoxicity, and hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages <15%.	HSR to ensure prompt reporting of reactions. • Obtain AST and ALT levels in patients with rash. Obtain AST and ALT levels at baseline, before dose escalation, 2 weeks after dose escalation, and thereafter at 3-month intervals. • Avoid NVP use in women with CD4 counts >250 cells/mm^3 and in men with CD4 counts >400 cells/mm^3, unless benefits outweigh risks. • Do not use NVP as PEP outside of the neonatal period.	would avoid the NNRTI drug class when restarting treatment.
	ETR	**Onset** • Any time during therapy **Presentation** • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.	• Rare	• Unknown	• Evaluate for hypersensitivity if the patient is symptomatic.	• Discontinue all ARV drugs. • Rechallenge with ETR **is not recommended.**
	MVC	• Rash preceding hepatotoxicity	• Rare	• Unknown	• Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	• Discontinue all ARV drugs. • Rechallenge with MVC **is not recommended.**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	• DTG	• Rash with hepatic dysfunction	• Rare	• Unknown	• Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	• Discontinue all ARV drugs. • Rechallenge with DTG is **contraindicated.**

[a] The prescribing information for NVP states that patients who experience rash during the 14-day lead-in period should not have the NVP dose increased until the rash has resolved. However, prolonging the lead-in phase beyond 14 days may increase the risk of NVP resistance because of subtherapeutic drug levels. Children who have persistent mild or moderate rash after the lead-in period should receive individualized care. Consult an expert in HIV care when managing these patients. **NVP should be stopped and not restarted** if the rash is severe or progressing. See the Nevirapine section of the Drug Appendix.

[b] Lead-in dosing **is not recommended** when using NVP for either presumptive or definitive HIV therapy in newborns with perinatal HIV exposure or perinatal HIV infection. See the Nevirapine section of the Drug Appendix and Table 12 in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Key: ABC = abacavir; ALT = alanine transaminase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; BIC = bictegravir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP2B6 = Cytochrome P450 Family 2 Subfamily B Member 6; DRESS = drug reaction (or rash) with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ETR = etravirine; FTC = emtricitabine; HLA = human leukocyte antigen; HLA-B*5701 = human leucocyte antigen gene variant; HSR = hypersensitivity reaction; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PEP = post-exposure prophylaxis; PI = protease inhibitor; PREDICT Study = Personalised Responses to Dietary Composition Trial Study; RAL = raltegravir; RPV = rilpivirine; SJS = Stevens-Johnson syndrome; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

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Management of Children Receiving Antiretroviral Therapy

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

In the United States, the majority of children with HIV are receiving antiretroviral therapy (ART), making treatment-experienced children the norm. Providers may consider antiretroviral (ARV) regimen changes for the following reasons:

- *Treatment simplification:* Modifying ARV regimens in children who are currently receiving effective ART in order to simplify the regimen.
- *Treatment optimization:* Increasing the treatment potency or barrier to resistance of an effective, but older or potentially fragile regimen or improving the adverse-event profile.
- *Toxicity management:* Recognizing and managing ARV drug toxicity or intolerance (see Management of Medication Toxicity or Intolerance).
- *Treatment failure:* Recognizing and managing treatment failure (see Recognizing and Managing Antiretroviral Treatment Failure).

Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy

Panel's Recommendations
• Children who have sustained virologic suppression on their current antiretroviral (ARV) regimen should be evaluated regularly for opportunities to change to a new regimen that facilitates adherence, simplifies administration, increases ARV potency or barrier to drug resistance, and decreases the risk of drug-associated toxicity **(AII).** • Before changing a patient's ARV regimen, clinicians must carefully consider the patient's previous regimens, past episodes of ARV therapy failure, prior drug-resistance test results, drug cost, and insurance coverage, as well as the patient's ability to tolerate the new drug regimen **(AIII).** Archived drug resistance can limit the antiviral activity of a new drug regimen. • Children should be monitored carefully after a change in treatment. Viral load measurement is recommended 2 to 4 weeks after a change in a child's ARV regimen **(BIII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Clinicians choose initial ARV regimens for children with HIV by evaluating the pharmacokinetic, safety, and efficacy data for the drugs that are available in formulations suitable for the child's age and weight at the start of treatment. New ARV drug options may become available as children grow and learn to swallow pills and as new drugs, drug formulations, and data become available. Even in cases wherein patients have achieved sustained virologic suppression (i.e., suppression for 6–12 months) on their current regimen, clinicians should consider switching patients to new ARV regimens to permit the use of pills instead of liquids, reduce pill burden, allow the use of once-daily medications, reduce the risk of adverse events, minimize drug interactions, and align a child's regimen with widely used, efficacious adult regimens.[1] These changes often enhance adherence and improve quality of life.[2]

Treatment Simplification

Many infants and children with HIV initiated treatment with twice-daily dosing (especially prior to the approval of integrase strand transfer inhibitor [INSTI] medications in children), and regimens included a variety of drug formulations, depending on which formulations were available for a child's age and weight. Clinicians should regularly review treatment options as children grow, because it may be possible to simplify dosing using coformulated drugs and/or once-daily regimens (see Table 16 below). Clinicians also should consider a child's ART history and drug-resistance test results. Small studies have shown that children who achieve virologic suppression using twice-daily dosing for certain ARV drugs (e.g., abacavir [ABC], nevirapine [NVP]) maintain virologic suppression when they are switched from twice-daily dosing to appropriate once-daily dosing of the same drugs (see the Abacavir and Nevirapine sections and fixed-dose combinations [FDCs] in Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets and Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Consideration for Use in Children and Adolescents). However, these studies reported mixed results when switching the dosing for lopinavir/ritonavir (LPV/r) from twice daily to once daily. Therefore, once-daily dosing of LPV/r **is not recommended.**[3-6] Once-daily dosing of NVP is available for some age groups, but most pediatric HIV experts would opt for more potent ARV options with a higher barrier to drug resistance and a better side-effect profile (see Table 16 below).

Treatment Optimization

The aims of treatment optimization may include improving the potency of the regimen, improving a child's growth or other health outcomes through reduced drug side effects and/or better treated HIV, or maximizing palatability. More studies are directly evaluating treatment optimization in children, and early results support the safety and efficacy of regimen switches for those with viral suppression. Older studies have demonstrated sustained viral suppression and improved growth outcomes in young children who have demonstrated good adherence and no baseline resistance and who were switched from LPV/r-based regimens to either an NVP-based regimen (NEVEREST 2 Trial) or an efavirenz (EFV)-based regimen (NEVEREST 3 Trial); however, many providers would not consider a switch to an NVP-based optimization regimen because of its low barrier to resistance and side-effect profile.[7-10] Likewise, replacing LPV/r with EFV may provide some benefits (e.g., once-daily dosing and a different side-effect profile), but most pediatric HIV experts would prefer replacing LPV/r with an equally potent protease inhibitor (PI) (e.g., darunavir [DRV], atazanavir [ATV]) or an INSTI (e.g., elvitegravir [EVG], raltegravir, dolutegravir [DTG], or bictegravir [BIC]), based on studies in adults and emerging evidence of noninferiority or superiority in children.[11,12] Although not a switch trial, preliminary findings from the randomized controlled Once-daily DTG based ART in Young People vs. Standard Therapy (ODYSSEY) study of more than 700 children aged <18 years in eight countries showed superior virologic and clinical outcomes in children randomized to optimization with DTG-based ART compared with those in the standard of care (PI- or non-nucleoside reverse transcriptase inhibitor [NNRTI]-based regimens), contributing to evidence supporting optimization with DTG-based regimens.[13] Additionally, several observational studies in sub-Saharan Africa that are evaluating efforts to optimize pediatric ARV regimens have shown improved viral suppression rates in children switched to DTG-based regimens[14-16]. Similarly, a retrospective study from six African countries reporting on 2,655 children aged 0 to ≤19 years demonstrated sustained high levels of viral suppression in children optimized from NNRTI- and PI-based regimens to DTG-based regimens[17]. Other INSTI-based regimens (including the FDCs BIC/emtricitabine (FTC)/tenofovir alafenamide (TAF) and EVG/cobicistat/FTC/TAF) also have shown efficacy and similar rates of long-term viral suppression in adolescents. Early results from small randomized studies also show potential for switches to newer-generation NNRTI medications—such as rilpivirine (RPV)[18] and doravirine (DOR)[19]—in children and adolescents weighing ≥35 kg who have been virologically suppressed on a stable ARV regimen.

Toxicity Management

Several studies of small cohorts of children have demonstrated sustained virologic suppression and reassuring safety outcomes when drugs that have greater long-term toxicity risks are replaced with drugs that are thought to have lower toxicity risks (e.g., replacing stavudine with tenofovir disoproxil fumarate, TAF, zidovudine, or ABC; replacing PIs with NNRTIs), including improved lipid profiles.[20-24] Similarly, adolescents who were switched from EFV to RPV, a newer generation of NNRTIs, showed similar rates of viral suppression with improved metabolic profiles and cognitive outcomes.[18] Additionally, studies in adults have shown improved tolerability, lipid profiles, and insulin sensitivity in patients who were switched from PIs to INSTIs,[25-29] and adults who were switched from EFV to an INSTI have shown improvement in neuropsychiatric symptoms. However, the use of INSTIs, as well as TAF, has been associated with weight gain in adults and adolescents, with emerging data showing an association in children.[30-34]

Treatment Failure

Treatment failure is another common reason providers change ARV regimens in children with HIV. This topic is covered in Recognizing and Managing Antiretroviral Treatment Failure.

Regimens That Are Not Recommended for Use in Children

Monotherapy PI regimens (DRV/r, LPV/r, ATV/r)[35,36] and monotherapy regimens of DTG[37,38] have been used to simplify or reduce the toxicity of regimens in adult patients who have sustained virologic suppression, but with varying success. These strategies are still being explored, but they are not currently recommended as management strategies in children because of the lack of data.[36,39-42]

Two-drug regimens, specifically nucleoside-sparing regimens, have shown efficacy in adults and are being studied in children and adolescents. The PENTA-17 SMILE study, which included 318 children aged 6 to 18 years in 11 countries, showed that DRV/r combined with an INSTI was noninferior in maintaining virologic suppression at 48 weeks in participants without an INSTI or PI resistance.[43] However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not currently recommend this investigational drug combination in children or adolescents. A similar two-drug FDC tablet containing DTG/RPV—a nucleoside-sparing, dual-therapy regimen that is marketed as Juluca—is approved by the U.S. Food and Drug Administration as a complete regimen to replace the current ARV regimen in adult patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months and who have no history of treatment failure. This approval was based on two Phase 3 clinical trials, SWORD-1 and SWORD-2, in which treatment-experienced adults who were virologically suppressed on three- or four-drug regimens were randomized either to switch to DTG/RPV (early-switch group) or to stay on their original regimens through 48 weeks and then switch to DTG/RPV (late-switch group). Results from these trials showed similar rates of virologic suppression in both groups (noninferiority) through 3 years of follow-up.[44-46] No equivalent data exist for this drug combination in pediatric patients. The Panel usually endorses the use of adult formulations in adolescents, and this product may be appropriate for certain adolescents. However, because this treatment simplification strategy has not been evaluated in adolescents who may have difficulties adhering to therapy, the Panel does not recommend the routine use of DTG/RPV or other nucleoside-sparing regimens in adolescents and children until more data are available.

Potential Antiretroviral Drug Switches in Children with Virologic Suppression

Table 16 below contains examples of potential ARV drug changes in children with sustained virologic suppression on their current regimen for the purpose of treatment simplification, optimization, or reduced toxicity. When considering such a change, a clinician should first ensure that a recent viral load test indicates that the child is not experiencing virologic failure and that the child has a reliable history of good adherence (assessed by self and parental report, pharmacy refill, prior viral loads, etc.). Among treatment-naive youth in the United States aged 13 to 24 years, some evidence exists that single-tablet regimens (STRs) improve the odds of viral suppression[47]; emerging evidence also supports the safety, efficacy, and tolerability of STRs in younger children.[48-50] Although these data have not been replicated in treatment-experienced adolescents, clinicians should consider using STRs in children and youth with sustained viral suppression, because these regimens reduce pill burden and dosing frequency. Clinicians also must consider ART history, tolerability, and all prior drug-resistance test results to avoid choosing new ARV drugs for which archived drug resistance would reemerge and limit the activity of the regimen.[51-55] The evidence that supports many of these ARV changes is indirect, that is, extrapolated from data about drug performance during initial therapy or follow-up therapy after treatment failure. When such changes are made, careful monitoring (e.g., taking a viral load measurement 2–4 weeks after making the switch to the new regimen) is important to ensure that virologic suppression is maintained.

Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression

This list is not exhaustive and does not necessarily contain all potential treatment options. Instead, it provides examples of changes that could be made. The table includes information only about switching between ARV drugs; **it does not include all the information that clinicians should consider before prescribing these drugs, such as drug cost and the patient's insurance coverage.** Refer to the individual drug sections, Table 1, and Table 2 in Appendix A: Pediatric Antiretroviral Drug Information for further information about the use of specific ARV drugs and FDC formulations.

Current ARV Drug(s)	Age, Weight, and Sexual Maturity Rating Requirements	Potential ARV Drug Switch[a]	Comment
NRTIs			
ABC Twice Daily	Aged ≥3 months[b]	ABC once daily	See the Abacavir[b] section.
3TC Twice Daily	Aged ≥3 years	3TC once daily	See the Lamivudine section.
	Any age (starting at full-term birth) Any weight	FTC once daily	See the Emtricitabine section.
ZDV	Aged ≥1 months[b]	ABC	Less long-term mitochondrial toxicity. Children aged ≥3 months can take ABC once daily.
	Weighing 17 kg to <25 kg	TDF	TDF is a reasonable, once-daily option for HLA-B*5701-positive children for whom ABC is not recommended and in whom ZDV is not tolerated. TDF is available as an oral powder and as low-strength tablets alone or in combination with FTC.
	Weighing ≥14 kg	TAF[c]	Less long-term mitochondrial toxicity. Once-daily dosing. Only available in coformulation with other ARV drugs; can further reduce pill burden. TAF is preferred over TDF because of the lower risk of bone and renal toxicity, but it may be associated with weight gain and lipid abnormalities.
NNRTIs			
NVP or EFV	Any age (starting at full-term birth) Weighing ≥2 kg	RAL[d]	RAL is preferred over NVP in infants from birth to age 4 weeks who weigh ≥2 kg. Both are dosed twice daily in children. Note that DTG and BIC both have higher barrier to resistance than RAL. In a child >1 month of age, DTG is preferred. See DTG below.

Current ARV Drug(s)	Age, Weight, and Sexual Maturity Rating Requirements	Potential ARV Drug Switch[a]	Comment
	Age ≥4 weeks Weighing ≥3 kg	DTG	DTG is available as a single drug in dispersible and film-coated tablet formulations, or as part of an FDC tablet, all of which can be dosed once daily if no documented resistance or history of failure with INSTI agents exists. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. DTG is available as a component of the FDC tablet ABC/DTG/3TC (Triumeq), which is a complete ARV regimen that can be given to children weighing ≥25 kg. Higher barrier to resistance, which makes it a good choice for patients who have poor adherence. May improve lipid levels. See the Dolutegravir section for more information.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	ATV/r has a potentially greater barrier to resistance; however, taking ATV/r may be difficult for some patients, as ATV oral powder must be mixed with food or a beverage before administration, and the palatability of the RTV oral solution is poor.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r has a potentially greater barrier to resistance. DRV/r is administered twice daily to patients aged <12 years but may be administered once daily in children aged ≥12 years who do not have any DRV resistance mutations. Note that the palatability of the RTV oral solution is poor when considering administering it to children not able to swallow tablets.
	Weighing ≥14 kg	BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC tablet EVG/c/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥35 kg	DOR	DOR is available in a once-daily FDC tablet DOR/3TC/TDF (Delstrigo). Fewer side effects than reported with EFV. It has continued activity in the setting of some NNRTI mutations.
	Aged ≥12 years Weighing ≥35 kg	RPV	Lower incidence of adverse lipid effects. May have fewer sleep disturbances and neuropsychiatric symptoms compared to EFV.
PIs			
LPV/r Twice Daily	Any age (starting at full-term birth) Weighing ≥2 kg	RAL[d]	Better palatability. RAL HD can only be given once daily in those weighing ≥40 kg. Unlike LPV/r, the use of RAL is not restricted to infants with a corrected gestational age of ≥42 weeks and a postnatal age of ≥14 days. RAL granules may be difficult to dose for some caregivers.

Current ARV Drug(s)	Age, Weight, and Sexual Maturity Rating Requirements	Potential ARV Drug Switch[a]	Comment
	Age ≥4 weeks Weighing ≥3 kg	DTG	Once-daily dosing if no documented resistance or history of failure with INSTI agents exists. May be better tolerated, and it can be given as a dispersible tablet in young children or an FDC tablet in children weighing ≥25 kg. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. May improve lipid levels. See the Dolutegravir section for more information.
	Aged ≥3 years Weighing ≥10 kg	EFV	Once-daily dosing. Better palatability. Lower incidence of adverse lipid effects. See the Efavirenz section for concerns about EFV dosing for children aged <3 years.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	Once-daily dosing. ATV/r may have a lower incidence of adverse lipid effects; however, taking ATV/r may be difficult for some patients, as ATV oral powder must be mixed with food or a beverage before administration, and the palatability of the RTV oral solution is poor.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r may have a lower incidence of adverse lipid effects. DRV/r is administered twice daily to patients aged <12 years, but it may be administered once daily in children aged ≥12 years who do not have DRV resistance mutations. Note that palatability of the RTV oral solution is poor when considering administering it to children not able to swallow tablets.
	Weighing ≥14 kg	BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC tablet EVG/c/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥35 kg	DOR	DOR is available in a once-daily FDC tablet DOR/3TC/TDF (Delstrigo). Fewer side effects than reported with EFV. It has continued activity in the setting of some NNRTI mutations.
	Aged ≥12 years Weighing ≥35 kg	RPV	May be better tolerated. Lower incidence of adverse lipid effects.
INSTIs			
RAL	Age >1 month and weighing <14 kg Weighing >14 kg	DTG DTG or BIC	Once-daily dosing. Higher barrier to resistance. DTG is available as a single drug in a dispersible tablet for infants and children weighing ≥3 kg; in a single-drug film-coated tablet for children weighing 14 kg; or as an FDC tablet. All of these can be dosed once daily if no documented resistance or history of failure with INSTI agents exists. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. DTG is available as a component of the FDC tablet ABC/DTG/3TC (Triumeq), which is a complete ARV regimen that can be given to children
EVG/c	Weighing ≥14 kg	DTG or BIC	

Current ARV Drug(s)	Age, Weight, and Sexual Maturity Rating Requirements	Potential ARV Drug Switch[a]	Comment
			weighing ≥25 kg. See the Dolutegravir section for more information. BIC has once-daily dosing and a higher barrier to resistance. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
Other			
Any Multi-Pill and/or Twice-Daily Regimen	Weighing ≥25 kg	EVG/c/FTC/TAF (Genvoya)	Once-daily dosing. Single pill. Alignment with adult ARV regimens. Must be taken with food.
	Weighing ≥14 kg	FTC/TAF[c] (Descovy) plus DTG	Once-daily dosing. This regimen may be more desirable because of smaller pill sizes, but it has a higher pill burden (two pills instead of one). Aligns a child's regimen with an efficacious regimen that is used in adults. See the Dolutegravir section for more information.
	Weighing ≥14 kg	BIC/FTC/TAF (Biktarvy)	Once-daily dosing. Single pill that can be taken with or without food.
	Weighing ≥25 kg	ABC/DTG/3TC (Triumeq)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Large pill size may be a deterrent. See the Dolutegravir section for more information.
	Weighing ≥35 kg SMR 4 or 5	EVG/c/FTC/TDF (Stribild)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food. Renal and bone toxicity of TDF limit its use.
	Aged ≥12 years Weighing ≥35 kg	FTC/RPV/TAF (Odefsey)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food at a consistent time daily.
	Aged ≥12 years Weighing ≥35 kg SMR 4 or 5	FTC/RPV/TDF (Complera)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food at a consistent time daily. Renal and bone toxicity of TDF limit its use.
	Weighing ≥35 kg	DOR/3TC/TDF (Delstrigo)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food at a consistent time daily. Renal and bone toxicity of TDF limit its use. Review NNRTI mutations and check for drug–drug interactions before use.

[a] The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for an adolescent. When discussing ART options with adolescents of childbearing potential and their caregivers, it is important to consider the benefits and risks of all ARV drugs and to provide the information and counseling needed to support informed decision-making; refer to the Perinatal Guidelines (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 5. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers).

[b] For infants and young children who are being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In clinically stable patients with undetectable viral loads who have had stable CD4 T lymphocyte cell counts on twice-daily ABC, the dose can be changed from twice daily to once daily. ABC is not approved by the U.S. Food and Drug Administration for use in neonates and infants aged <3 months. Recent data from the IMPAACT P1106 trial and two

observational cohorts provide reassuring evidence of the safety of ABC in infants aged <3 months. Based on these data, clinicians may consider the use of ABC in infants aged ≥1 month to <3 months, in consultation with a pediatric HIV specialist (see Abacavir).

[c] For children and adolescents weighing ≥14 kg to <35 kg, TAF can be used in combination with an INSTI or an NNRTI, but **not** a boosted PI. For children and adolescents weighing ≥35 kg, TAF can be used in combination with an INSTI, an NNRTI, or a boosted PI.

[d] RAL is recommended for twice-daily use in children. Chewable tablets can be used as dispersible tablets starting at 4 weeks of age. RAL HD once daily is **only** recommended for virologically suppressed children weighing ≥40 kg.

Key: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; DOR = doravirine, DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HD = high dose; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Recognizing and Managing Antiretroviral Treatment Failure

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• The causes of antiretroviral (ARV) treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug–drug interactions—should be assessed and addressed **(AII).** • Perform ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen **(AI*)** (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines for more information). • ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results **(AI*).** • The new regimen should include at least two, but preferably three, fully active ARV medications; the assessment of anticipated ARV activity should be based on treatment history and past resistance test results **(AII*).** • The goal of therapy following treatment failure is to achieve and maintain virologic suppression, which is defined as a plasma viral load that is below the limits of detection as measured by highly sensitive assays with lower limits of quantification of 20 copies/mL to 75 copies/mL **(AI*).** • When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent the development of additional drug resistance that could further limit future ARV drug options **(AII).** • Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist **(AI*).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Categories of Treatment Failure

Treatment failure can be categorized as virologic failure, immunologic failure, clinical failure, or some combination of the three. Immunologic failure refers to a suboptimal immunologic response to therapy or an immunologic decline while on therapy, but no standardized definition exists. Clinical failure is defined as the occurrence of new opportunistic infections (OIs) (excluding immune reconstitution inflammatory syndrome [IRIS]) and/or other clinical evidence of HIV disease progression during therapy. Almost all antiretroviral (ARV) management decisions for treatment failure are based on addressing virologic failure.

Virologic Failure

Virologic failure refers to either an incomplete initial response to therapy or a viral rebound after virologic suppression is achieved. *Virologic suppression* is defined as having a plasma viral load below the lower level of detection, as measured by highly sensitive assays with lower limits of quantitation of 20 copies/mL to 75 copies/mL. *Virologic failure* is defined as repeated instances of a plasma viral load ≥200 copies/mL after 6 months of therapy. Laboratory results must be confirmed with repeat testing before a final assessment of virologic failure is made.

Infants with high plasma viral loads at initiation of ART occasionally take longer than 6 months to achieve virologic suppression. Because of this, some experts continue the treatment regimen for infants if their viral load is declining but is still ≥200 copies/mL at 6 months. These infants should be monitored closely until they achieve virologic suppression.[1] However, ongoing nonsuppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)–based regimens—increases the risk of drug resistance.[2,3]

The clinical implications of HIV RNA levels that are between the lower level of detection and <200 copies/mL in patients on antiretroviral therapy (ART) remain unclear. Adults with HIV who have detectable viral loads and a quantified result <200 copies/mL after 6 months of ART generally achieve virologic suppression without changing regimens.[4,5] However, some studies in adults have found that multiple viral load measurements of 50 copies/mL to <200 copies/mL (sometimes characterized as low-level viremia) may be associated with an increased risk of later virologic failure.[6-9] In contrast, a recent study that followed a cohort of 57 adult patients with low-level viremia (21–200 copies/mL) reported that none of the patients had resistance to their regimens, and all had adequate plasma ARV concentrations. At 96 weeks of follow-up, 67% remained with low-level viremia, 26% had viral loads <20 copies/mL, and only 7% had viral failure; none was attributed to viral resistance.[10]

"Blips"—defined as isolated episodes of a detectable but low level of plasma viral load (i.e., <500 copies/mL) that are followed by a return to viral suppression—are common and not generally reflective of short-term virologic failure, although they may indicate an increased risk of virologic failure after 12 to 24 months.[11-13] However, repeated or persistent plasma viral loads that are ≥200 copies/mL (especially viral loads that are >500 copies/mL) in patients who have previously achieved virologic suppression usually indicate virologic failure.[5,13-15]

In a cohort of children from Cambodia, Indonesia, Malaysia, Thailand, and Vietnam who were on first-line combination therapy,[16] among those who achieved viral suppression (<50 copies/mL on two successive measurements), 17% had at least one viral load with low-level viremia over a median follow-up of 6 years. More than a third of those had repeated episodes of low-level viremia. The rate of viral failure was 8.9 per 100 patient-years in those with low-level viremia versus 3.3 per 100 patient-years in those without low-level viremia. Of note, 97% of the cohort were started on an NNRTI-based regimen, which has a lower barrier to resistance than other regimens and, therefore, may not be generalizable to patients on other regimens.

Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.[17] Patients with baseline severe immunosuppression (i.e., a CD4 T lymphocyte [CD4] cell count <500 cells/mm^3) often take longer than 1 year to achieve immune recovery, even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur. In an international study, 12% of pediatric and adolescent patients had a poor immunologic response 1 year after viral suppression (defined as <400 copies/mL), although poor immunologic response dropped to 7% at 2 years and 3% at 3 years in those with continued viral suppression. Among those with a poor immunologic response at 1 year post viral suppression, a fourfold increased risk of an AIDS diagnosis or death was observed, compared with immune responders (rate ratio 4.04; 95% confidence interval, 1.83–8.92; $P < 0.001$).[18]

In cases of poor immunologic response despite virologic suppression, clinicians should first exclude laboratory error in CD4 values or viral load measurements and ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 count that occurs during the first 5 to 6 years of life. Another laboratory consideration is that some viral load assays may not amplify all HIV groups and subtypes (e.g., HIV-1 non-M groups, HIV-2), resulting in falsely low or negative viral load results (see Diagnosis of HIV Infection in Infants and Children and Clinical and Laboratory Monitoring of Pediatric HIV Infection). Once laboratory results are confirmed, clinicians should evaluate patients for adverse events, medical conditions, and other factors that can cause CD4 values to decrease (see Table 17 below).

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and conditions (e.g., hepatitis C virus [HCV], tuberculosis [TB], malnutrition, Sjogren's syndrome, sarcoidosis, syphilis, cirrhosis, acute viral infections) are independently associated with low CD4 values.[19]

Patients who have very low baseline CD4 values before initiating ART are at higher risk of an impaired CD4 response to ART and, based on data from adult studies, may be at higher risk of death and AIDS-defining illnesses despite virologic suppression.[20-22] In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 348 children (37%) had CD4 counts <500 cells/mm^3 at ART initiation, including 92 (9.9%) who had CD4 counts <200 cells/mm^3. After 1 year of virologic suppression, only seven children (1% of the cohort) failed to reach a CD4 count ≥200 cells/mm^3, and 86% of children had CD4 counts >500 cells/mm^3. AIDS-defining events were uncommon overall (occurring in 1% of participants), but they occurred both in children who achieved improved CD4 counts and those who did not.[17] Studies in adults with HIV note that CD4 count recovery at 1 year and 2 years post-initiation of initial therapy is independent of the drug class used, that is, boosted protease inhibitor (PI), integrase strand transfer inhibitor (INSTI), or NNRTI.[23]

In summary, poor immunologic response to treatment can occur. Management consists of confirming that CD4 values and viral load measurements are accurate, avoiding the use of drugs that are associated with low CD4 values, and treating other conditions that could impair CD4 recovery. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** modifying an ARV regimen based on lack of immunologic response if virologic suppression is confirmed.

Poor Clinical Response Despite Adequate Virologic and Immunologic Responses

Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunologic and virologic responses to ART; not all cases represent ART failure. At times, after initiation of ART, patients will suffer a clinical deterioration due to paradoxical worsening of a known OI or unmasking of a previously undiagnosed OI due to a profound immune response (i.e., IRIS) related to successful viral suppression. This does not represent ART treatment failure and does not generally require discontinuation of or a change in ART. IRIS does not mean that ART has failed, and it does not generally require discontinuation of ART.[24,25] Children who have suffered irreversible damage to their lungs, brain, or other organs—especially during prolonged and profound pre-treatment immunosuppression—may continue to have recurrent infections or symptoms in the damaged organs, because the immunologic improvement may not reverse damage to the organs.[26] Such cases do not represent ART failure, and these children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should be evaluated to rule out (and, when indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary TB, malnutrition, and malignancy.

Occasionally, however, children will develop new HIV-related OIs (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis that occurs more than 6 months after achieving markedly improved CD4 values and virologic suppression) that are not related to IRIS, pre-existing organ damage, or another cause.[17] Although such cases are rare, they may represent ART clinical failure, and improvement in CD4 values may not necessarily normalize immunologic function. In children who have signs of new or progressive abnormal neurodevelopment, some experts change the ARV regimen, aiming to include agents that are known to achieve higher concentrations in the central nervous system. However, the data regarding the effectiveness of this strategy are inconclusive.[27,28]

Table 17. Discordance Among Virologic, Immunologic, and Clinical Responses

Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression
Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response • Laboratory error (in CD4 value or viral load measurement) • Misinterpretation of normal, age-related CD4 count decline (i.e., the immunologic response is not actually poor) • Low pre-treatment CD4 count or percentage • AEs that are associated with the use of certain drugs (e.g., ZDV, TMP-SMX, systemic corticosteroids) • Use of systemic corticosteroids or chemotherapeutic agents • Conditions that can cause low CD4 values (e.g., HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis)
Poor Immunologic and Clinical Responses Despite Virologic Suppression • Laboratory error (in CD4 value or viral load measurement) • Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (i.e., HIV-1 non-M groups, HIV-1 non-B subtypes, HIV-2 [although this is unusual with newer viral load assays]) • Persistent immunodeficiency that occurs soon after initiating ART, but before ART-related reconstitution • Primary protein-calorie malnutrition • Untreated TB • Malignancy
Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses
• IRIS • A previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy) • Malnutrition • Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy, worsening neurodevelopmental delay), lungs (e.g., bronchiectasis), cardiac (i.e., cardiomyopathy), renal (i.e., HIV-related kidney disease) • A new clinical event due to a non-HIV illness or condition • A new, or otherwise unexplained, HIV-related clinical event (e.g., treatment failure)

Key: AEs = adverse effects; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Management of Virologic Failure

The approach to managing and subsequently treating virologic failure will differ, depending on the etiology of the problem. When assessing a child with suspected virologic failure, clinicians should evaluate therapy adherence and medication intolerance, confirm that the prescribed dosing is correct (and understood by the child and/or caregiver) for all medications in the regimen, consider possible pharmacokinetic (PK) interactions that might lead to low drug levels, and test for possible drug resistance (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Although many factors can contribute to virologic failure, the main barrier to sustained virologic suppression in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations that confer partial or complete resistance to one or more components of the ARV regimen. See Adherence to Antiretroviral Therapy in Children and Adolescents with HIV for guidance on assessing adherence and strategies for improving adherence.

Virologic Failure with No Antiretroviral Drug Resistance Identified

Persistent viremia in the absence of detectable viral resistance to current medications is usually a result of nonadherence, but it is important to consider other factors, such as poor drug absorption, incorrect dosing, and drug interactions. If adequate drug exposure can be ensured, then adherence to the current regimen should result in virologic suppression. Resistance testing should take place while a child is on therapy. After discontinuing therapy, plasma viral strains may quickly revert to wild type and reemerge as the predominant viral population, in which case, resistance testing can fail to identify the drug-resistant virus (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). In this situation, resistance can be identified by restarting the prior medications while emphasizing adherence and repeating resistance testing in 4 weeks if plasma virus remains detectable. If the HIV plasma viral load becomes undetectable, then nonadherence was likely the original cause of virologic failure.

Virologic failure in children receiving boosted PI-based regimens is frequently associated with no detected major PI-resistance mutations.[29] Virologic suppression may be achieved by continuing the PI-based regimen, implementing adherence-improvement measures, and addressing any PI-related side effects.[30-32] However, continued virologic failure on PI-based regimens—especially if PI drug levels are subtherapeutic or in the presence of nucleoside reverse transcriptase inhibitors (NRTIs)-resistance mutations—can lead to major PI mutations.[33]

In some cases, if a new, more convenient regimen could address the main barrier to adherence, it may be reasonable for a clinician to switch a patient to this new regimen (e.g., a single fixed-dose combination [FDC] tablet taken once daily) while closely monitoring adherence and viral load. Similarly, if an ART side effect or tolerability is found to be impacting adherence, switching to a new regimen with close monitoring should be considered. However, in cases where clinicians determine that patients have poor adherence to the current regimen and that adherence is unlikely to improve with a new regimen, clinicians should focus on improving adherence before initiating a new regimen (see Adherence to Antiretroviral Therapy in Children and Adolescents with HIV).

Virologic Treatment Failure with Antiretroviral Drug Resistance Identified

After deciding that a change in therapy is necessary, a clinician should attempt to identify at least two, but preferably three, fully active ARV agents from at least two different drug classes to use in a patient's new regimen. The clinician should consider all of the patient's past and recent drug-resistance test results, the patient's prior exposure to ARV drugs, whether the patient is likely to adhere to the regimen, and whether the patient finds a particular regimen acceptable.[34-38] This process often requires using agents from one or more drug classes that are new to the patient. However, clinicians should be aware that drug-resistance mutations can confer cross-resistance within a drug class, so a drug that is new to the patient may still have diminished antiviral potency. Substituting or adding a single drug to a failing regimen **is not recommended,** because this is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. When reviewing results of drug-resistance assays, clinicians should consult the Stanford University HIV Drug

Resistance Database to determine if a change in the ARV regimen is required and, if a change is required, which ARV agents can be retained.

The process of switching a patient to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient and the patient's caregivers. This discussion should be appropriate for the patient's age and stage of development. Clinicians should be aware that some medications have conflicting food requirements and concomitant medication restrictions that may complicate the administration of a regimen. Timing of medication administration is particularly important, because it helps ensure adequate ARV drug exposures throughout the day. Palatability, pill size, number of pills, and dosing frequency all need to be considered when choosing a new regimen.[39]

Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure

A pediatric HIV specialist should be consulted when determining which new regimen will have the best chance of achieving complete virologic suppression in children who have already experienced treatment failure.

ARV regimens should be chosen based on a patient's treatment history and drug-resistance test results to optimize ARV drug potency in the new regimen (see Adherence to Antiretroviral Therapy in Children and Adolescents with HIV). A general strategy for regimen changes is shown in Table 18 below; however, as additional agents are licensed and studied for use in children, newer regimens that are better tailored to the needs of each patient may be constructed.

Data from adult and pediatric studies support the efficacy of a regimen that contains a boosted PI plus two NRTIs for those who experience treatment failure on an initial NNRTI-based regimen.[40] Studies of adults have found that a regimen that contains both a boosted PI and raltegravir (RAL) produces similar outcomes to a regimen that contains a boosted PI and two NRTIs.[40,41]

A clinical trial in adults who had experienced treatment failure on an initial NNRTI-based regimen reported that dolutegravir (DTG) had better efficacy and a better safety profile than lopinavir/ritonavir (LPV/r), when these drugs were used in second-line regimens that included at least one active NRTI.[42] Pediatric and adolescent data support the use of two NRTIs plus an INSTI, following the failure of an NNRTI-based regimen.[43-45]

However, caution should be exercised when considering the use of regimens that include first-generation INSTIs with a lower barrier to resistance (e.g., RAL), because children who experience treatment failure on NNRTI-based regimens often have substantial NRTI resistance.[46]

Resistance to the NNRTI nevirapine (NVP) results in cross-resistance to the NNRTI efavirenz (EFV), and vice versa. The NNRTIs etravirine (ETR) and rilpivirine (RPV) can retain activity against NVP-resistant virus or EFV-resistant virus in the absence of certain key NNRTI mutations), but ETR has generally been tested only in regimens that also contain a boosted PI.[34,47] For this reason, the Panel recommends using ETR as part of a regimen that includes a ritonavir-boosted PI (see the Etravirine section). Doravirine is a once-daily NNRTI that retains activity against EFV/NVP-resistant virus and was recently approved by the U.S. Food and Drug Administration (FDA) for use in children and adolescents weighing ≥35 kg. Studies are ongoing in adolescents aged 12 to 18 years[48] (see the Doravirine section).If a child experiences virologic failure on an initial PI-based regimen, there are often limited resistance mutations detected, indicating that poor adherence/tolerance of the regimen may be the cause of poor viral control.[46,49] In these cases, an alternative PI that might be potent and better tolerated can be used. For example, LPV/r-based regimens have been shown to have durable ARV activity in some PI-experienced children.[50-52] Darunavir (DRV)/r-based therapy also has been used.[53,54] Switching to an INSTI-based regimen also can be effective in some PI-experienced children.[43,45,55-57] When making the switch from a failing PI-based regimen to an INSTI-based regimen, preference might be given to the second-generation INSTIs DTG or bictegravir (BIC), because these drugs have a higher barrier to resistance than the first-generation INSTIs RAL and elvitegravir.

The availability of newer drugs within existing drug classes and the introduction of new classes of drugs increase the likelihood of finding three active drugs, even for children with extensive drug resistance (see Table 18 below). As previously discussed, INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI-based regimens or PI-based regimens.[43,45] RAL is the INSTI that has been studied and used most often in children, but both DTG and BIC have the advantage of once-daily dosing, small pill size, and higher barrier to development of drug resistance; they also often retain ARV activity in patients who have experienced treatment failure on RAL-based therapy (see the Dolutegravir and Bictegravir sections for the latest age and weight indications).[58] Early data about the use of DTG around the time of conception showed a small significant increase in the prevalence of infant neural tube defects (NTDs) that has declined over time. In the most recent analysis, the prevalence of NTDs did not differ significantly between women receiving DTG and non-DTG ARV regimens at the time of conception[59]. For additional information when prescribing DTG or other ARVs for adolescents of childbearing potential, see the Dolutegravir section and refer to the Perinatal Guidelines (see Recommendations for Use of Antiretroviral Drugs During Pregnancy and Appendix C. Antiretroviral Counseling Guide for Health Care Providers).

Maraviroc, a CCR5 antagonist, provides a new drug class; however, many ART-experienced children and a number of ART-naive children already harbor CXCR4-tropic virus, which precludes its use.[60,61] Regimens that include an INSTI and a potent boosted PI with or without ETR have been effective during small studies of extensively ART-experienced patients with multiclass drug resistance.[62-65] It is important to review individual drug profiles for information about drug interactions and dose adjustments when devising a regimen for children with multiclass drug resistance. Appendix A: Pediatric Antiretroviral Drug Information provides detailed information on drug formulations, pediatric and adult doses, and toxicity, as well as discussions of the available data on the use of ARV drugs in children.

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if drug resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching to a new formulation, such as an FDC tablet).

Some studies in adults have suggested that lamivudine (3TC) can still contribute to suppression of HIV replication in patients with 3TC resistance mutations. Continuation of 3TC also can maintain a 3TC mutation (184V) that can partially reverse the effects of other mutations that confer resistance to zidovudine and tenofovir disoproxil fumarate.[66-68]

Studies have compared the use of NRTI-sparing and NRTI-containing regimens in adults with multidrug resistance who experienced virologic failure on a previous regimen. These studies have demonstrated no clear benefit of including NRTIs in the new regimen.[69,70] One of these studies reported no difference in rate of virologic suppression but a trend toward a higher mortality in adults who were randomized to receive a regimen that included NRTIs than in adults who were randomized to receive an NRTI-sparing regimen.[70] There are no studies of NRTI-sparing regimens in children with virologic failure and multidrug resistance, but an NRTI-sparing regimen may be a reasonable option for children with extensive NRTI resistance.

Enfuvirtide (T-20) is approved by the FDA for use in ART-experienced children aged ≥6 years, but it must be administered by subcutaneous injection twice daily.[71,72] Regimens that contain more than three drugs (up to three PIs and/or two NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug–drug interactions.[73] The availability of agents with an increased barrier to resistance—such as the PI DRV, the second-generation NNRTIs ETR and RPV, and newer INSTIs DTG and BIC—have lessened the need for T-20, dual-PI regimens, and regimens of four or more drugs.

Two agents that inhibit the attachment of the glycoprotein (gp) 120 region of the virus to the CD4 molecule are approved for adolescents >18 years with multidrug resistance. Oral fostemsavir is a gp120 attachment inhibitor, and ibalizumab (given by infusion twice monthly) is a humanized monoclonal antibody that targets the gp120 attachment area on the CD4 molecule.[74,75] Because these represent drugs with new novel targets, they would be expected to be beneficial in patients with multiclass drug resistance.

When searching for at least two fully active agents in cases of extensive drug resistance, clinicians should consider the potential availability of new therapeutic agents that are not currently being studied in children or that may be approved for use in children in the future. Information about clinical trials can be found using the National Institute of Allergy and Infectious Diseases database and by consulting a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified; ideally, this would be done in the framework of a clinical trial. Expanded access programs or clinical trials may be available (see ClinicalTrials.gov). New drugs should be used in combination with at least one, but ideally two, additional active agents.

Pediatric dosing for off-label use of ARV drugs is problematic, because absorption, hepatic metabolism, and excretion change with age.[76] In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child's body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.[77]

Off-label use of ARV agents, however, may be necessary for children with HIV who have limited ARV drug options. In this circumstance, consulting a pediatric HIV specialist for advice about potential regimens, assistance with access to unpublished data from clinical trials or other limited off-label pediatric use, and referral to suitable clinical trials are recommended.

Management Options When Two Fully Active Agents Cannot Be Identified or Administered

It may be impossible to provide an effective and sustainable therapeutic regimen when there is no combination of currently available agents that are active against an extensively drug-resistant virus in a patient or when a patient is unable to adhere to or tolerate ART.

The decision to continue a nonsuppressive regimen must be made on an individual basis after weighing potential benefits and risks. Specifically, providers must balance the inherent tension between the benefits of virologic suppression and the risks of continued viral replication with potential evolution of viral drug resistance in the setting of inadequate ARV drug exposure (e.g., nonadherence or a nonsuppressive, suboptimal regimen). Nonsuppressive regimens could decrease viral fitness and, thus, slow clinical and immunologic deterioration while a patient is either working on adherence or awaiting access to new agents that are expected to achieve sustained virologic suppression.[78] However, persistent viremia in the context of ARV drug pressure has the potential to generate additional resistance mutations that could further compromise agents in the same class that might otherwise have been active in subsequent regimens (e.g., continuing first-generation INSTIs or NNRTIs). Patients who continue to use nonsuppressive regimens should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive ARV regimen should be reassessed at every opportunity.

The use of NRTI-only holding regimens or a complete interruption of therapy **is not recommended.** One trial, International Maternal Pediatric Adolescents AIDS Clinical Trials (IMPAACT P1094) randomized children with the M184V resistance mutation and documented nonadherence to continue their nonsuppressive, non-NNRTI-based regimen or to switch to a 3TC (or emtricitabine) monotherapy-holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 count (the primary outcome) over a 28-week period.[79]

Complete treatment interruption also has been associated with immunologic declines and poor clinical outcomes,[80,81] therefore, it **is not recommended** (see Antiretroviral Treatment Interruption in Children with HIV).

Table 18. Options for Regimens with at Least Two Fully Active Agents to Achieve Virologic Suppression in Patients with Virologic Failure and Evidence of Viral Resistance

To optimize antiretroviral (ARV) drug effectiveness, clinicians should evaluate a patient's treatment history and drug-resistance test results when choosing a new ARV regimen. Doing so is particularly important when selecting the nucleoside reverse transcriptase inhibitor (NRTI) components of an non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, where drug resistance to the NNRTI can occur rapidly if the virus is not sufficiently sensitive to the NRTIs. 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 emtricitabine and lamivudine is present, these medications should be continued if the new regimen contains tenofovir disoproxil fumarate, tenofovir alafenamide, or zidovudine. The presence of this mutation may increase susceptibility to these NRTIs.

Please see individual drug profiles for information about weight and age limitations (e.g., do not use darunavir in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance (see Appendix A: Pediatric Antiretroviral Drug Information). Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multiclass drug resistance. Regimens in this table are provided as examples, but the list is not exhaustive.

Prior Regimen	New Regimen Options[a]
Two NRTIs plus an NNRTI	Two NRTIs plus an INSTI[b] Two NRTIs plus a boosted PI
Two NRTIs plus a PI	Two NRTIs plus an INSTI[b] Two NRTIs plus a different boosted PI INSTI plus a different boosted PI with or without an NNRTI and with or without NRTI(s) Two NRTIs plus an NNRTI[c]
Two NRTIs plus an INSTI	Two NRTIs plus a boosted PI DTG[a,b] or BIC[a,b] (if not used in the prior regimen) with a boosted PI with or without one or two NRTIs. DTG must be given twice daily if a patient has certain documented INSTI mutations, or if there is concern about certain mutations (see the Dolutegravir section). Two NRTIs plus an NNRTI[c]
Failed regimen(s) that included NRTI(s), NNRTI(s), and PI(s)	**If NRTIs Are Fully Active** • INSTI plus two NRTIs **If NRTIs Are Not Fully Active** • INSTI plus two NRTIs with or without an RTV-boosted PI **If There Is Minimal NRTI Activity** • INSTI with or without an RTV-boosted PI with or without ETR, or RPV with or without NRTI(s) • Consider adding T-20 and/or MVC if additional active drug(s) are needed. • Consider off-label use of approved agents or enrollment in clinical trials for novel antiretroviral treatments.

[a] The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for an adolescent. When discussing ART options with adolescents of childbearing potential and their caregivers, it is important to consider the benefits and risks of all ARV drugs and to provide the information and counseling needed to support informed decision-making; refer to the Perinatal Guidelines (see Recommendations for Use of Antiretroviral Drugs During Pregnancy, Table 5 Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive, and Appendix C: Antiretroviral Counseling Guide for Health Care Providers).

[b] Raltegravir has a low barrier to resistance and requires twice-daily dosing in children and adolescents; BIC and DTG have a higher barrier to resistance and only require once-daily dosing. Many Panel members would use bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) in patients with prior treatment failure who have virus with the M184 mutation (see the Bictegravir section).

[c] NNRTIs could be an option in younger patients with no exposure to NNRTIs and with taste aversion to boosted PIs.

Key: BIC = bictegravir; DTG = dolutegravir; ETR = etravirine; INSTI = integrase strand transfer inhibitor; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide

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Antiretroviral Treatment Interruption in Children with HIV

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Panel's Recommendations
• Outside the context of clinical trials, structured interruptions of antiretroviral therapy **are not recommended** for children **(AII).**
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional* ***Rating of Evidence:*** *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion* *† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Unplanned Treatment Interruptions

Temporary discontinuation of antiretroviral therapy (ART) may be unavoidable in some situations—such as in cases of serious treatment-related toxicity, acute illnesses, or planned surgeries—that preclude oral intake. Lack of available medication also may result in temporary ART discontinuation. In resource-limited settings, children might experience interruptions due to drugs being out of stock locally. Children with HIV who are immigrating to the United States may also experience gaps in medication availability. Prolonged interruptions of ART also can result from disengagement from care or other social or psychological issues that affect adherence. Some patients, particularly adolescents and young adults, might attempt to conceal long periods of treatment interruption by restarting treatment in the few weeks ahead of clinic visits and viral load testing.

Observational studies of children and youth with unplanned or nonprescribed treatment interruptions suggest that interruptions are common, that most patients will experience immunologic decline during the treatment interruption, and that most patients will restart therapy.[1-4] In a retrospective study of 483 children in a French pediatric cohort from the National Agency for Research on AIDS and Viral Hepatitis (ANRS) , 42% of participants had treatment interruptions of ≥3 months (with a median of 12.1 months). Interruption was associated with lower CD4 T lymphocyte (CD4) cell percentages after 4 years, even in those who restarted therapy.[5] A similar retrospective study of 136 youth (median age 12.9 years) in the United States found that 38 participants (28%) with histories of treatment interruption had lower CD4 counts and higher HIV RNA levels than participants who had continuous treatment.[6]

Whether unplanned interruptions occur by accident or necessity (e.g., because of toxicity), all efforts should be made to minimize their duration. If a child will be traveling for an extended period, clinicians can help prevent treatment interruption by ensuring that the child will have access to the necessary drugs during the trip. If the required drugs will not be available at the destination, pharmacies can be asked to dispense extra medication. Additional guidance on supporting adherence can be found in Adherence to Antiretroviral Therapy in Children and Adolescents with HIV.

Structured Treatment Interruptions

Structured treatment interruptions are scheduled periods of time during which ART is not prescribed or administered. This strategy was once considered a method for providing patients with time off ART to reduce the risk of toxicity and costs. Randomized clinical trials of adults with HIV have demonstrated that structured treatment interruptions are associated with significantly higher morbidity and mortality than continuous ART.[7] Current U.S. Department of Health and Human Services HIV treatment guidelines recommend against planned, long-term structured treatment interruptions in adults (see Discontinuation or Interruption of Antiretroviral Therapy in the Adult and Adolescent Antiretroviral Guidelines).

Few studies have evaluated structured treatment interruption in children. In one trial from Europe and Thailand (PENTA 11), 109 children (median age 9 years) on ART and with virologic suppression were randomized to receive continuous therapy (CT) or to undergo treatment interruption. Although no significant differences in rates of adverse events (AEs) were observed between the two groups at 2 years, 19 of 56 children (34%) in the structured treatment interruption arm met CD4 criteria to restart therapy between 6 and 42 weeks after interruption, suggesting that the time off ART provided by this strategy was ultimately limited.[8,9] The Children with HIV Early Antiretroviral Therapy (CHER) trial in South Africa was designed to determine whether infants who initiated ART early could safely discontinue therapy at either 40 weeks or 96 weeks; infants would reinitiate treatment based on CD4 decline. The median time to the start of continuous ART after interruption was 33 weeks (interquartile range [IQR] 26–45 weeks) among the infants who discontinued ART after 40 weeks, and 70 weeks (IQR 35–109 weeks) among the infants who discontinued ART after 96 weeks.[10,11] A secondary analysis of neurodevelopmental outcomes at age 5 years did not show any significant differences among the children in the different study arms.[12] However, brain magnetic resonance imaging studies in a subset of participants found that children with HIV on interrupted ART (n = 21) had a thicker cortex than uninfected controls in the left frontal and right insular regions, but children with HIV on CT (n = 25) showed no difference from controls.[13] In another randomized trial, 12 of 21 infants in the treatment interruption arm met ART restart criteria within 3 months.[14] In summary, although trials of structured treatment interruptions in children have not shown significant short-term morbidity, the gains in time off ART are limited, and the long-term outcomes remain unknown.

The case of an infant from Mississippi who initiated ART soon after birth and had a prolonged period of time without viremia after an unplanned treatment interruption raised the hope that it may be possible to stop or reduce the intensity of ART (e.g., use fewer agents) in some infants (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV).[15,16] However, the “Mississippi infant” had documented viral rebound after 28 months off ART,[17] and additional reports have emerged of infants who experienced rebound viremia after stopping ART, despite having undetectable HIV DNA and RNA while on ART.[18-20] A South African child aged 9.5 years was reported to have low levels of virus that was not replication competent after receiving ART from approximately 2 to 24 months of age; the factors that led to this outcome remain unknown.[21] Future research might identify treatment strategies and diagnostic tests that enable ART to be safely interrupted in some children. “Analytical” treatment interruptions are currently being incorporated into studies of remission in adults and children, but the potential risks and benefits of strategies need to be critically evaluated.[22-24]

Currently, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** treatment interruption as a strategy in clinical settings to confirm diagnosis or to assess remission or cure in infants who reverted to negative serology, tested negative for HIV DNA, or received an initial diagnosis that was based on a single positive nucleic acid test. The Panel encourages providers to consult an expert on pediatric HIV when they are concerned about the validity of the test results that led to treatment initiation in children with HIV.

Short-Cycle Therapy Strategies

One approach, called short-cycle therapy (SCT), schedules 4-day treatment interruptions, rather than waiting to restart ART after CD4 count declines or other AEs occur. In one proof-of-concept study (ATN015), 32 participants (aged 12–24 years) underwent short cycles of 4 days on and 3 days off ART.[25] Participants received protease inhibitor–based ART and had at least 6 months of documented viral suppression (defined as a viral load <400 copies/mL) and CD4 counts above 350 cells/mm^3. Most participants demonstrated good adherence to the schedule, but 12 participants (37.5%) developed confirmed viral load rebounds >400 copies/mL, and 18 participants (56%) left the study. SCT had no impact on CD4 counts.

The BREATHER (PENTA 16) study sought to examine the safety and benefits of SCT with 5 days on and 2 days off ART; PENTA 16 was a noninferiority trial that randomized 199 children and young adults (aged 8–24 years) for SCT or CT.[26,27] To enroll, participants had to be receiving efavirenz (EFV) plus two nucleoside reverse transcriptase inhibitors, and they had to have been virologically suppressed (defined as a viral load <50 copies/mL) for >12 months. By 48 weeks, six participants (6%) in the SCT arm and seven participants (7%) in the CT arm experienced confirmed virologic failure, which was defined as a viral load >50 copies/mL (difference −1.2%; 90% confidence interval, −7.3% to 4.9%). Of the six participants in the SCT arm who experienced virologic failure, five were able to regain virologic suppression. Two participants in the SCT arm and five participants in the CT arm had major mutations related to resistance to non-nucleoside reverse transcriptase inhibitors at the time of virologic failure. At 48 weeks, the SCT arm had higher D-dimer levels but no other evidence of increased inflammation across a number of other biomarkers. Participants generally reported appreciating the option of SCT.[28]

A long-term follow-up study of children from the BREATHER study (which included 194 of the original 199 children) suggests comparable virologic failure rates between the SCT and CT arms after a median of 3.6 years; both arms had a failure rate of approximately 16%.[29] The participants in the SCT arm experienced a greater number of serious AEs than participants in the CT arm (20 serious AEs in the SCT arm versus 8 in the CT arm, with the primary difference being rate of hospitalizations); however, the arms experienced comparable rates of Centers for Disease Control and Prevention– Grade 3 or 4 AEs. The BREATHER trial suggests that SCT with EFV-based ART may be safe in some adolescents and may yield increased patient satisfaction that could lead to better long-term adherence. However, the Panel believes that additional data are needed to decide whether this strategy would be safe in different patient populations, with different antiretroviral (ARV) regimens, outside of the context of a trial, and over longer periods.

Conclusion

Most studies have shown that treatment can be safely interrupted in children with HIV only for short periods. Furthermore, treatment interruption yields minimal potential benefits to counterbalance the risks associated with the use of this strategy, and long-term follow-up data are limited. One benefit of treatment interruptions was the potential reduction of toxicity; however, current ARV agents have lower toxicity than older ARV drugs. It is possible that SCT strategies may be safe for some patients, but additional data are needed to support the use of these strategies. Currently, the Panel **does not recommend** structured treatment interruption in the clinical care of children with HIV; additional studies of treatment-interruption strategies in specific situations are warranted.

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Appendix A: Pediatric Antiretroviral Drug Information

Overview

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs)

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Protease Inhibitors (PIs)

Entry and Fusion Inhibitors

Integrase Inhibitors (INSTIs)

Pharmacokinetic Enhancers

Fixed-Dose Combinations

Antiretrovirals Available in Fixed-Dose Combination Tablets

Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents

Archived Drugs

Didanosine

Enfuvirtide

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Stavudine

Tipranavir

Appendix A: Pediatric Antiretroviral Drug Information

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Tenofovir Alafenamide (TAF, Vemlidy)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

Abacavir (ABC, Ziagen)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Pediatric Oral Solution: 20 mg/mL ***Tablet:*** *300 mg (scored)* *Generic Formulations* • 300 mg tablet • 20 mg/mL pediatric oral solution *Fixed-Dose Combination Tablets* • [Epzicom and generic] Abacavir 600 mg/lamivudine 300 mg • [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg *When using fixed-dose combination (FDC) tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.* *For additional information, see Drugs@FDA or DailyMed.*

Dosing Recommendations	Selected Adverse Events
Neonate (Aged Birth Through <1 Month) Dose *Oral Solution* • Abacavir (ABC) is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates aged <1 month. • The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends ABC 2 mg/kg twice daily for full-term infants from birth through <1 month of age. This recommendation is based on data from pharmacokinetic (PK) modeling of neonatal ABC dosing to target adult plasma ABC exposures, and observational data supporting safety of ABC in neonates. The World Health Organization (WHO) HIV guidelines Annex 1: Dosages for ARV Drugs provide weight-band dosing recommendations for full-term neonates based on the same data (see Approval, Pharmacokinetics in Neonates and Infants, and Safety in Neonates and Infants sections below). **Infant (Aged ≥1 Month to <3 Months) Dose** *Oral Solution* • ABC is not approved by the FDA for use in infants aged <3 months.	• Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough, shortness of breath). **Special Instructions** • Test patients for the HLA-B*5701 allele before starting therapy to predict the risk of HSRs. Patients who test positive for the HLA-B*5701 allele should not be given ABC. Patients with no prior HLA-B*5701 testing who are tolerating ABC do not need to be tested. • Warn patients and caregivers about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of ABC. Do not rechallenge.** • ABC can be given without food. The oral solution does not require refrigeration. • Screen patients for hepatitis B virus (HBV) infection before using ABC FDC tablets that contain lamivudine (3TC). Severe acute exacerbation of HBV infection can occur when 3TC is discontinued, see Lamivudine.

- The Panel recommends ABC 4 mg/kg twice daily in full-term infants aged ≥1 month to <3 months. This recommendation is based on modeling data of the ABC 4 mg/kg twice-daily dose using PK simulation for full-term infants aged ≥1 month to <3 months. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1106 study and two observational cohorts provide reassuring data on the safety of ABC in infants with HIV aged <3 months. See Approval, Pharmacokinetics in Neonates and Infants, and Safety in Neonates and Infants sections below.

Infant and Child (Aged ≥3 Months) Dose

Oral Solution

- ABC 8 mg/kg twice daily (maximum 300 mg per dose) or ABC 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In older children who can be treated with tablet formulations, therapy can be initiated with once-daily administration. In clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte counts while receiving the liquid formulation of ABC twice daily, the ABC dose can be changed from twice daily to once daily with the liquid or tablet formulations (see text below).

Weight-Band Dosing for Children and Adolescents Weighing ≥14 kg

Weight	Scored 300-mg Tablet		
	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
≥20 kg to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1½ tablets (450 mg)
≥25 kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 mg)

Child and Adolescent (Weighing ≥ 25 kg) and Adult Dose

- ABC 300 mg twice daily or ABC 600 mg once daily

[Epzicom] Abacavir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:

- One tablet once daily

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily

Metabolism/Elimination

- ABC is systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.
- The majority of ABC is excreted as metabolites in urine.

Abacavir Dosing in Patients with Hepatic Impairment

- ABC requires a dose adjustment in patients with mild hepatic insufficiency and is contraindicated with moderate or severe hepatic insufficiency.
- **Do not use** Epzicom and Triumeq (or the generic equivalents of these FDC tablets) in patients with impaired hepatic function, because the dose of ABC cannot be adjusted.

Abacavir Dosing in Patients with Renal Impairment

- ABC does not require dose adjustment in patients with renal impairment.
- **Do not use** Epzicom and Triumeq (or the generic equivalents of these FDC tablets) in patients with creatinine clearance <50 mL/min or patients on dialysis, because the doses of 3TC (in all three FDCs) cannot be adjusted.

• This FDC tablet can be used in patients who are antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor–naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers. • The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing ≥40 kg (see Dolutegravir for more information).	

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Abacavir (ABC) neither inhibits nor is metabolized by hepatic cytochrome P450 enzymes. Therefore, it does not cause significant changes in the clearance of agents that are metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors.
- ABC plasma concentrations can decrease when ABC is used concurrently with the ritonavir-boosted PIs atazanavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir.[1-3] The mechanism and the clinical significance of the drug interactions with these PIs are unknown. Currently, no recommendations exist for dose adjustments when ABC is coadministered with one of these boosted PIs.
- Alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) interferes with ABC metabolism; it affects the activity of alcohol dehydrogenase and glucuronyl transferase. This interference increased ABC area under the curve (AUC) plasma exposure by 41% in adult men with HIV who received ABC 600 mg daily.[4]
- ABC oral solution contains sorbitol, which decreased the exposure of lamivudine (3TC) oral solution in adults when the drugs were administered concurrently.[5]

Major Toxicities

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, anorexia
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) have been observed in approximately 5% of adults and children (the rate varies by race/ethnicity) receiving ABC. HSRs generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of ABC. The risk of an ABC HSR is associated with the presence of the HLA-B*5701 allele; the risk is greatly reduced by not using ABC in those who test positive for the HLA-B*5701 allele. The HSR to ABC is a multiorgan clinical syndrome usually characterized by rash, or signs or symptoms in two or more of the following groups:
  - Fever
  - Constitutional symptoms, including malaise, fatigue, or achiness
  - Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhea, or abdominal pain
  - Respiratory signs and symptoms, including dyspnea, cough, or pharyngitis
  - Laboratory and radiologic abnormalities, including elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and

severe hepatomegaly with steatosis—including fatal cases—also have been reported. Pancreatitis with laboratory abnormalities can occur.

If an HSR is suspected, ABC **should be stopped immediately and not restarted because hypotension and death may occur upon rechallenge.**

- *Rare:* Increased levels of liver enzymes, elevated blood glucose levels, elevated triglycerides (see cardiovascular risk below). Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis—including fatal cases—have been reported.
- *Rare*: Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome.
- *Rare:* Several observational cohort studies suggest that an increased risk of myocardial infarction exists in adults who are currently using ABC or who have recently used ABC; however, other studies have not substantiated this finding, and no prospective data are available on the cardiovascular risks associated with ABC use in children. One cohort study of South African adolescents (in which 385 participants had HIV and 63 participants were HIV-negative controls) with a median age of 12 years reported an association between ABC exposure and insulin resistance, which was evaluated using homeostatic model assessment. These findings suggest that the use of ABC may be a cardiovascular risk factor for young people with perinatally acquired HIV.[6]

Resistance

The International Antiviral Society–USA (IAS-USA) maintains a list of updated HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ABC is approved by the U.S. Food and Drug Administration (FDA) for use in children with HIV aged ≥3 months as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The World Health Organization (WHO), however, provides dosing guidance for ABC as a component of the NRTI backbone for full-term neonates starting at birth and weighing ≥2 kg (see Annex 1: Dosages for ARV Drugs in the WHO HIV guidelines). The WHO guidance for ABC dosing in neonates increases the choices of antiretroviral (ARV) agents for the management of newborns in special situations where stock outs of nevirapine or zidovudine (ZDV) may affect the ability to effectively provide postnatal prophylaxis or treatment of neonatal HIV. The WHO recommendation of ABC dosing for infants starting at 1 month of age is based on the inclusion of ABC as a preferred NRTI component of the first- and second-line ARV regimens for children in the WHO HIV guidelines. This recommendation also takes into account the availability of the President's Emergency Plan for AIDS Relief (PEPFAR) tentatively approved pediatric generic ABC formulations—including coformulations that include 3TC—and the cost of ARV drugs in resource-limited settings.

Efficacy

Both the once-daily and twice-daily doses of ABC have demonstrated durable antiviral efficacy in pediatric clinical trials that is comparable to the efficacy observed for other NRTIs in children.[7-11]

Pharmacokinetics

Pharmacokinetics in Neonates and Infants

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1106 trial reported PK data in 25 infants aged <3 months who were initiated on a median ABC dose of 10 mg/kg (range, 6–13 mg/kg) twice daily in combination with lamivudine and lopinavir/ritonavir. Median age was 6 weeks (range, 1.5–11 weeks); median weight was 2,250 g (range, 1,360–3,320 g); median gestational age was 36 weeks (range, 27–39 weeks). Sparse and pre-dose PK ABC samples were repeatedly obtained throughout 24 weeks of study follow-up, and population PK modeling was applied. ABC plasma exposures were high compared to the published data in infants aged >3 months and decreased rapidly between 2 and 8 months of age as the infants matured and ABC clearance increased.[12]

PK modeling of ABC starting at birth has been conducted using pooled data from 308 ABC concentration measurements obtained from three studies administering ABC liquid to 45 young infants (including 21 full-term neonates <15 days of age with intensive PK).[13] Two of these studies, the Pediatric AIDS Clinical Trials Group (PACTG) 321 study and Tygerberg cohort, performed intensive PK sampling in full-term neonates receiving ABC for HIV prophylaxis. The third study, IMPAACT P1106, performed sparse PK sampling on full-term and low-birth weight ([LBW] <2,500 g) infants with HIV, initiating ABC-based ART after 1 month of age. LBW infants were older at the first PK assessment, with a median postnatal age of 78 days (range, 41–190) and weight of 3.6 kg (range, 2.4–5.8). ABC PK parameters in neonates were estimated using PK simulations to achieve plasma ABC exposures (AUC_{0-12}) within the expected adult range (3.2–25.2 mcg•hr/mL). ABC elimination was greatly reduced at birth but rapidly increased during the first weeks of life. Simulations predicted that an ABC dose of 2 mg/kg twice daily in full-term neonates from birth to <4 weeks and an ABC dose of 4 mg/kg twice daily in infants aged 4 to 12 weeks would achieve target AUC_{0-12}; however, data in LBW infants are lacking.[13] Based on these data, the weight-band dosing of ABC for neonates has been developed for neonates from birth to age <1 month and is included in the WHO HIV Guidelines Annex 1: Dosages for ARV Drugs.[14] This weight-band dosing for neonates approximates the ABC dosing per kg based on the postnatal age (see Table 1 below).

Table 1. Simplified Weight-Band Dosing for Full-Term Neonates from Birth to <1 Month of Age (WHO HIV guidelines Annex 1: Table A1.4)

Birth to <1 Month of Age		
Weight	**Volume of ABC Oral Solution 20 mg/mL Twice Daily**[a,b]	**ABC Dose in mg Twice Daily** (ranges mg/kg, from lowest to highest weight within the weight band)[a,b]
2 kg to <3 kg	0.4 mL	8 mg (4.0–2.8 mg/kg)
3 kg to <4 kg	0.5 mL	10 mg (3.3–2.6 mg/kg)
4 kg to < 5 kg	0.6 mL	12 mg (3.0–2.4 mg/kg)

[a] Simplified weight-band dosing exceeds recommended mg/kg ABC dosing in neonates and infants.

[b] Neonatal ABC dose is based on birth weight and does not require weight-based adjustment during the first month of life.

Key: ABC = Abacavir

For infants aged ≥1 month with weight 3 to <6 kg, the WHO HIV guidelines currently recommend a twice-daily dose of 3 mL (60 mg) of ABC 20 mg/mL solution (range, 20.0–10.2 mg/kg). The weight-band dosing for neonates and infants within the WHO HIV guidelines is higher than the modeled weight-based dosing for practical considerations in resource-limited settings. As new, generic pediatric formulations of ABC become available in resource-limited settings, there is potential for the revision of the WHO weight-band dosing of ABC for young infants.

Based on the PK modeling from three infant studies[13] and the neonatal and infant safety data from IMPAACT 1106 study and two observational cohort studies (see Safety in Neonates and Infants below), the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends an ABC dose of 2 mg/kg twice daily for neonates from birth to <1 month of age and an ABC dose of 4 mg/kg twice daily for full-term infants aged ≥1 month and <3 months.

Pharmacokinetics in Children

PK studies of ABC in children aged <12 years have demonstrated that metabolic clearance of ABC in adolescents and young adults (aged 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.[15]

The PKs of ABC administered once daily in children with HIV aged 3 months through 12 years were evaluated in three crossover, open-label PK trials of twice-daily versus once-daily dosing of ABC and 3TC (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).[4,16-19] The data from these three pediatric trials were used to develop a model for ABC PKs; this model predicted that systemic plasma ABC exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged ≤12 years.[16-20] Both these trials and PK modeling have demonstrated that once-daily dosing with either the tablet or the liquid formulation of ABC produces plasma exposures comparable to those seen with a twice-daily dosing schedule that uses the same total daily dose of ABC.[4]

Dosing

Dosing and Formulations

Initially, the recommended dose for pediatric use was ABC 8 mg/kg twice daily for a total of 16 mg/kg per day. A 2015 FDA review suggested that a total daily dose of ABC 600 mg could be used safely in a person weighing 25 kg (i.e., ABC 24 mg/kg per day, a 50% increase from the previously recommended dose). The weight-band dosing table recommends total daily doses as high as ABC 21.5 mg/kg per day to ABC 22.5 mg/kg per day when treating patients with the tablet formulation.[4] No difference is seen in the ABC plasma C_{max} and area under the curve for the ABC liquid formulation compared to the tablet formulation.[21] Doses of the liquid ABC formulation are similar to those used for weight-band dosing with tablet formulations and should be considered for use in younger children who are unable to swallow a pill.

In the three ABC dosing pediatric trials described above,[16-19] only children who had low viral loads and who were clinically stable on the twice-daily dose of ABC were eligible to change to once-daily ABC dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily ABC (n = 336) versus twice-daily ABC (n = 333) in tablet form combined with a once-daily or twice-daily 3TC-based ARV regimen.[11] To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of the ABC liquid formulation. In children who can be treated with pill formulations, initiating therapy with once-daily dosing of ABC at a dose of 16 mg/kg (with a maximum dose of ABC 600 mg) is recommended. However, twice-daily dosing is recommended for infants and young children who initiate therapy with the liquid formulation of ABC. Switching to once-daily dosing with the liquid or pill formulation could be considered in clinically stable children with suppressed viral loads and stable CD4 T lymphocyte counts.

Toxicity

Safety in Neonates and Infants

Recent data from the IMPAACT P1106 trial and two observational European and African cohorts provided reassuring data on the safety of ABC in infants when initiated at <3 months of age, including infants with weight <3 kg.[12,22,23] The IMPAACT P1106 trial reported 24 weeks of safety data in 25 infants who initiated ABC at the median age of 6 weeks. Of the 25 infants, one infant died of unknown cause 3 days after entry. Fourteen infants had Grade 3/4 adverse events (AEs); the most common were gastroenteritis (n = 4) and respiratory infection (n = 4). No hypersensitivity was reported. All AEs were assessed as unrelated to ABC, except for one possibly related Grade 2 alanine aminotransferase in which all ARVs were stopped for 2 weeks until resolution and were restarted without further complications.[12] The European Pregnancy and Paediatric Infections Cohort Collaboration (EPPICC) reported safety outcomes among 139 children from 13 cohorts in 11 countries in Europe who initiated ABC at age <3 months. By 12 months on ABC, 3.6% (n = 4) had discontinued ABC because of an ART safety concern and 11.8% (n =15) discontinued ABC for any reason.[22] Another observational study of nine cohorts from the International Epidemiology Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration compared safety outcomes between infants who started ABC aged <28 days (n = 96) and those aged ≥28 days (n = 835) and between infants who started ABC with weight <3 kg (n = 246) and those with weight ≥3 kg (n = 53).[23] ABC discontinuations at 6 and 12 months were not significantly different in infants who started ART aged <28 days and ≥28 days or in infants who weighed <3 kg and ≥3 kg.[23]

ABC has less of an effect on mitochondrial function than the NRTI ZDV[7,8] and less bone and renal toxicity than tenofovir disoproxil fumarate.[24,25]

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Emtricitabine (FTC, Emtriva)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Pediatric Oral Solution: 10 mg/mL **Capsule: 200 mg** **Fixed-Dose Combination (FDC) Tablets** • [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg • [Biktarvy] ○ Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg ○ Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg • [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg • [Descovy] ○ Emtricitabine 200 mg/tenofovir alafenamide 25 mg ○ Emtricitabine 120 mg/tenofovir alafenamide 15 mg • [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg • [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg • [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg • [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg • [Truvada] ○ Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg ○ Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg ○ Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg ○ Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg **When using FDC tablets, refer to other sections of the** Drug Appendix **for information about the individual components of the FDC. See also** Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents**.** **For additional information, see** Drugs@FDA **or** DailyMed**.**

Dosing Recommendations	Selected Adverse Events
Neonatal and Infant (Aged 0 to <3 Months) Dose *Oral Solution* • Emtricitabine (FTC) 3 mg/kg once daily **Child (Aged ≥3 Months) and Adolescent Dose**	• Hyperpigmentation/skin discoloration on palms and/or soles

Oral Solution

- FTC 6 mg/kg once daily (maximum 240 mg per dose). The maximum dose of oral solution is higher than the capsule dose, because a pediatric pharmacokinetic analysis reported that the plasma exposure for FTC was 20% lower in patients who received the oral solution than in patients who received the capsule formulation.

Capsules (For Patients Weighing >33 kg)

- FTC 200 mg once daily

Adult Dose

Oral Solution for Patients Who Are Unable to Swallow Capsules

- FTC 240 mg (24 mL) once daily

Capsules

- FTC 200 mg once daily

[Atripla and Generic] Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

[Biktarvy]

Bictegravir/Emtricitabine/Tenofovir Alafenamide (TAF)

Neonate or Child (Aged <2 Years and Weighing <14 kg) Dose

- No data are available on the appropriate dose of Biktarvy in children aged <2 years and weighing <14 kg. Studies are currently being conducted to identify the appropriate dose for this age and weight group.

Child, Adolescent, and Adult Dose

- One tablet once daily, with or without food.

Body Weight	Dose
≥14 to <25 kg	Bictegravir 30 mg/emtricitabine 120 mg/ tenofovir alafenamide 15 mg
≥25 kg	Bictegravir 50 mg/emtricitabine 200 mg/ tenofovir alafenamide 25 mg

- The U.S. Food and Drug Administration approved Biktarvy for use only in antiretroviral therapy (ART)-naive patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Biktarvy. Some members of the Panel

Special Instructions

- Although FTC can be administered without regard to food, some FDC tablet formulations that contain FTC have food requirements.
- FTC oral solution can be kept at room temperature, up to 77°F (25°C), if used within 3 months; refrigerate oral solution for long-term storage.
- Screen patients for hepatitis B virus (HBV) infection before using FTC or FDC tablets that contain FTC. Severe acute exacerbation of HBV infection can occur when FTC is discontinued; therefore, hepatic function and hepatitis B viral load should be monitored for several months after patients with HBV infection stop taking FTC.

Metabolism/Elimination

- No cytochrome P450 interactions
- Eighty-six percent of FTC is excreted in urine. FTC may compete with other compounds that undergo renal elimination.

Emtricitabine Dosing in Patients with Hepatic Impairment

- Atripla should be used with caution in patients with hepatic impairment.
- Biktarvy, Genvoya, Stribild, and Symtuza are not recommended for use in patients with severe hepatic impairment.
- Complera, Descovy, and Odefsey do not require dose adjustment in mild or moderate hepatic impairment, but should not be used in patients with severe hepatic impairment, because they have not been studied in this group.

Emtricitabine Dosing in Patients with Renal Impairment

- Decrease the dose of FTC in patients with impaired renal function. Consult the manufacturer's prescribing information for recommended dose adjustments.
- **Do not use** the FDC tablets Atripla or Complera in patients with creatinine clearance (CrCl) <50 mL/min or in patients who require dialysis.
- **Do not use** the FDC tablets Truvada or Biktarvy in patients with CrCl <30 mL/min. Do not use Truvada in patients who require dialysis.
- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- TAF-containing formulations are not recommended for use in patients with estimated CrCl <30 mL/min.

on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation. • See the Bictegravir section for additional information. **[Complera]** **Emtricitabine/Rilpivirine/TDF** *Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose* • One tablet once daily in ART-naive patients who have baseline plasma HIV RNA ≤100,000 copies/mL. This dose of Complera also can be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA <50 copies/mL) with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera. • Administer with a meal of at least 500 calories. **[Descovy]** **Emtricitabine/TAF** *Child and Adolescent and Adult Dose*	

Body Weight	Dose
≥14 kg to <25 kg	FTC 120 mg/TAF 15 mg, in combination with an integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). In this weight band, Descovy should not be used with protease inhibitors (PIs) that require a cytochrome P450 (CYP) 3A inhibitor (e.g., ritonavir [RTV] or cobicistat [COBI]).
≥25 kg to <35 kg	FTC 200 mg/TAF 25 mg, in combination with an INSTI or an NNRTI. In this weight band, Descovy should not be used with PIs that require a CYP3A inhibitor (i.e., RTV or COBI).
≥35 kg	FTC 200 mg/TAF 25 mg, in combination with an INSTI, NNRTI, or boosted PI.

[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/TAF

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily with food in ART-naive patients. This dose of Genvoya also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

[Odefsey]

Emtricitabine/Rilpivirine/TAF

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose

- One tablet once daily in ART-naive patients with HIV RNA ≤100,000 copies per mL. This dose of Odefsey also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.
- Administer with a meal of at least 500 calories.

[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF

Child and Adolescent (Weighing ≥35 kg with a Sexual Maturity Rating of 4 or 5) and Adult Dose

- One tablet once daily with food in ART-naive patients. This dose of Stribild also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.

[Symtuza]

Darunavir/Cobicistat/Emtricitabine/TAF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily with food in ART-naive patients or in patients who have been virologically suppressed (HIV RNA <50 copies/mL) with no known mutations associated with resistance to darunavir or tenofovir.

[Truvada]

Emtricitabine/TDF (FTC/TDF)

Child, Adolescent, and Adult Dose

Truvada Dosing Table

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	One FTC 100 mg/TDF 150-mg tablet
22 kg to <28 kg	One FTC 133 mg/TDF 200-mg tablet
28 kg to <35 kg	One FTC 167 mg/TDF 250-mg tablet
≥35 kg and adults	One FTC 200 mg/TDF 300-mg tablet

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* **Do not use** emtricitabine (FTC) in combination with lamivudine (3TC), because these agents share similar resistance profiles and lack additive benefit. **Do not use FTC** with fixed-dose combination (FDC) medications that contain 3TC or FTC. See Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets and refer to other sections of the Drug Appendix for drug interaction information for each individual component of an FDC tablet.
- *Renal elimination:* FTC may compete with other compounds that undergo renal tubular secretion. Drugs that decrease renal function could decrease clearance of FTC.

Major Toxicities

- *More common:* Headache, insomnia, diarrhea, nausea, rash. Hyperpigmentation/skin discoloration, which may be more common in children than in adults.
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in patients with hepatitis B virus (HBV)/HIV coinfection who switched from regimens that included FTC to regimens that did not include FTC.

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

FTC is approved by the U.S. Food and Drug Administration for once-daily administration in children, starting at birth. FTC often is used as part of a dual-NRTI backbone in antiretroviral (ARV) regimens for children and adolescents because of its once-daily dosing, minimal toxicity, and favorable pediatric pharmacokinetic (PK) data.

Efficacy and Pharmacokinetics

Comparative Clinical Trials

Studies that assess the efficacy and/or potency of nucleoside/nucleotide analogues have been more concerned with the dynamic components of the regimen—such as tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or abacavir—than the more static components, such as FTC or 3TC. FTC and 3TC have been considered to be interchangeable, but data to support this conclusion are lacking. Investigators studying the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort compared the efficacy of TDF plus FTC with TDF plus 3TC when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in antiretroviral therapy (ART)-naive patients.[1] The adjusted hazard ratio for the virologic failure of 3TC-containing regimens compared with FTC-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). No difference between these regimens was observed in the time to virologic suppression during the first 48 weeks of therapy or time to virologic failure after attaining suppression. In a Swiss cohort, Yang et al. found a potential difference in efficacy between FTC and 3TC; however, the difference disappeared after adjusting for pill burden.[2] Current evidence suggests that FTC and 3TC have equivalent efficacy and toxicity in ARV-naive patients.

Efficacy

Following a dose-finding study by Wang et al. (described in the Pharmacokinetics: Liquid Versus Capsule section below),[3] a once-daily dose of FTC 6 mg/kg administered in combination with other ARV drugs was studied in 116 patients aged 3 months to 16 years.[4] The study used a maximum dose of 240 mg of the FTC liquid formulation. PK results showed that the plasma exposures seen in these children and adolescents were similar to those seen in adults who received FTC 200 mg once daily. Follow-up data extending to Week 96 indicated that 89% of ART-naive children and 76% of ARV-experienced children maintained plasma HIV RNA <400 copies/mL (75% of ARV-naive children and 67% of ARV-experienced children had HIV RNA <50 copies/mL). Minimal toxicity was observed during this trial. Pediatric AIDS Clinical Trials Group (PACTG) P1021[5] evaluated the use of FTC 6 mg/kg (with a maximum dose of FTC 200 mg per day of the liquid formulation) as part of a three-drug regimen dosed once daily to ARV-naive children aged 3 months to 21 years. In this trial, 85% of children achieved HIV RNA <400 copies/mL, and 72% of children maintained virologic suppression (HIV RNA <50 copies/mL) through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm^3 at Week 96.

Pharmacokinetics: Liquid Versus Capsule

A single-dose PK study of the FTC oral solution and FTC capsules enrolled 25 children with HIV aged 2 years to 17 years.[3] FTC was found to be well absorbed following oral administration, with a mean elimination half-life of 11 hours (range, 9.7–11.6 hours). Plasma concentrations in children who received the once-daily dose of FTC 6 mg/kg were approximately equivalent to those seen in adults who received the standard dose of FTC 200 mg. However, plasma concentrations of FTC after administration of the capsule formulation were approximately 20% higher than those observed after administration of the oral solution in this small cohort of children.

Pharmacokinetics in Infants

A study in South Africa evaluated the PKs of FTC in 20 infants aged <3 months with perinatal HIV exposure. The participants received a dose of FTC 3 mg/kg once daily for two 4-day courses, separated by an interval of ≥2 weeks.[6] FTC exposure (area under the curve [AUC]) in neonates receiving FTC 3 mg/kg once daily was within the range of exposures seen in pediatric patients aged >3 months who received the recommended dose of FTC 6 mg/kg once daily and adults who received the recommended once-daily dose of FTC 200 mg. During the first 3 months of life, FTC AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (n = 6) who received a single dose of FTC 3 mg/kg and whose mothers received a single dose of FTC 600 mg during delivery, the FTC AUC exceeded the AUC seen in adults and older children. However, FTC had a half-life of 9.2 hours in these neonates, which is similar to that observed in adults and older children.[7] Extensive safety data are lacking for this age range.

Considerations for Use

The FTC oral solution has an advantage over the liquid formulation of 3TC, because it can be given once daily at ARV initiation, whereas the liquid formulation of 3TC needs to be given twice daily at ARV initiation. When pill formulations of 3TC or FTC are used, they can be administered once daily.

Both FTC and 3TC have antiviral activity and efficacy against HBV. For a comprehensive review of this topic, see the Hepatitis B Virus section in the Pediatric Opportunistic Infection Guidelines.

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Lamivudine (3TC, Epivir)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Pediatric Oral Solution • [Epivir] 10 mg/mL • [Epivir HBV][a] 5 mg/mL **Tablets** • [Epivir] 150 mg (scored) and 300 mg • [Epivir HBV][a] 100 mg **Generic Formulations** • 100-mg, 150-mg, and 300-mg tablets **Fixed-Dose Combination (FDC) Tablets** • [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg • [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg • [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg • [Dovato] Dolutegravir 50 mg/lamivudine 300 mg • [Epzicom] Abacavir 600 mg/lamivudine 300 mg • [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg • [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg • [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg • [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg • [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Note: See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection and Table 12: Antiretroviral Dosing Recommendations for Newborns for information about using lamivudine (3TC) to prevent perinatal HIV transmission.	• Headache **Special Instructions** • 3TC can be given without regard to food. • Store 3TC oral solution at room temperature. • Screen patients for hepatitis B virus (HBV) infection before using 3TC or FDC tablets that

Neonate (≥32 Weeks Gestation at Birth) and Infant (Birth to <4 Weeks) Dose

Oral Solution

- 3TC 2 mg/kg twice daily

Infant and Child Dose

- Once-daily dosing of the 3TC oral solution **is not recommended** when initiating 3TC oral solution in infants and young children. Patients can be transitioned to once-daily treatment with the oral solution when they have been stable on twice-daily treatment for 36 weeks and are aged ≥3 years. Please see the note below and refer to the text for more detail.

Aged ≥4 Weeks to <3 Months

- 3TC 4 mg/kg twice daily of the oral solution

Aged ≥3 Months to <3 Years

- 3TC 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose)

Aged ≥3 Years

- 3TC 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose); *or*
- 3TC 10 mg/kg once daily of the oral solution (maximum 300 mg per dose)

Weight-Band Dosing for the 10-mg/mL Lamivudine Oral Solution in Children Weighing ≥3 kg

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM
3 kg to <6 kg	3 mL	3 mL
6 kg to <10 kg	4 mL	4 mL
10 kg to <14 kg	6 mL	6 mL

Weighing ≥14 kg and Able to Swallow Tablets

- Weight-band dosing (see table below; dose is approximately 3TC 5 mg/kg per day twice daily or 3TC 10 mg/kg once daily)
- The scored tablet is the preferred formulation for pediatric patients weighing ≥14 kg who can swallow a tablet.

contain 3TC. Severe acute exacerbations of HBV can occur after discontinuation of lamivudine. Hepatic function and HBV viral load should be monitored for several months after patients with HBV infection stop taking 3TC. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection.

Metabolism/Elimination

Lamivudine Dosing in Patients with Hepatic Impairment

- No change in 3TC dosing is required for patients with hepatic impairment.
- FDC tablets containing abacavir (ABC) or zidovudine (ZDV) should not be used in patients who have impaired hepatic function.
- Symfi and Symfi Lo should be used in with caution in patients with hepatic impairment; Symfi and Symfi Lo are not recommended for use in moderate or severe hepatic impairment.
- Delstrigo and Dovato do not require dose adjustment in mild or moderate hepatic impairment but have not been studied in patients and so are not recommended with severe hepatic impairment.

Lamivudine Dosing in Patients with Renal Impairment

- Dose adjustment of 3TC is required for patients with renal insufficiency.
- FDC tablets containing 3TC should not be used in patients who have creatinine clearance <50 mL/min or are on hemodialysis.

Weight-Band Dosing for the Scored, 150-mg Lamivudine Tablet in Children Weighing ≥14 kg

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to <20 kg	½ tablet (75 mg)	½ tablet (75 mg)	1 tablet (150 mg)
≥20 kg to <25 kg	½ tablet (75 mg)	1 tablet (150 mg)	1½ tablets (225 mg)
≥25 kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets (300 mg)

Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports switching from twice-daily dosing to once-daily dosing of 3TC (using the oral solution or tablets) in children aged ≥3 years who have been clinically stable for 36 weeks with undetectable viral loads and stable CD4 T lymphocyte cell counts. Clinicians should choose a once-daily regimen using the once-daily dose of 3TC indicated above (approximately 3TC 10 mg/kg, with a maximum of 3TC 300 mg once daily).

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- 3TC 150 mg twice daily; *or*
- 3TC 300 mg once daily

[Cimduo] Lamivudine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing >35 kg) and Adult Dose

- One tablet once daily

[Combivir and Generic] Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥30 kg) and Adult Dose

- One tablet twice daily

[Delstrigo] Doravirine/Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily in ARV-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Delstrigo.

[Dovato] Dolutegravir/Lamivudine

Adult Dose

- One tablet once daily with or without food as a complete antiretroviral (ARV) regimen in antiretroviral therapy (ART)–naive adults with no known mutations associated with resistance to the individual components of Dovato.

- Dovato is not approved by the U.S. Food and Drug Administration (FDA) or recommended by the Panel for use in children or adolescents as a complete ARV regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug.

[Epzicom] Abacavir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily

[Symfi] Efavirenz 600 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily on an empty stomach

[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily on an empty stomach
- Symfi Lo has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in efavirenz (EFV) plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh ≥40 kg. The use of therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh ≥40 kg (see the Efavirenz section for more information).

[Temixys] Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily

[Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily
- This FDC tablet can be used in patients who are ART-naive or ART-experienced (but integrase strand transfer inhibitor naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing ≥40 kg (see the Dolutegravir section for more information).

[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine

Child and Adolescent (Weighing ≥30 kg) and Adult Dose

- One tablet twice daily

[a] Epivir HBV oral solution and tablets contain a lower amount of 3TC than Epivir oral solution and tablets. The amount of 3TC in the Epivir HBV solution and tablet was based on dosing for treatment of HBV infection in people without HIV coinfection.

Patients with HIV who are taking Epivir HBV as part of their ARV regimen should receive the appropriate amount of oral solution or the appropriate number of tablets to achieve the higher doses of 3TC that are used to treat HIV.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Drugs that decrease renal function could decrease clearance of lamivudine (3TC).
- **Do not use** 3TC in combination with emtricitabine (FTC), because these drugs have similar resistance profiles and using them together offers no additional benefit.[1] **Do not use** 3TC with fixed-dose combination (FDC) medications that contain 3TC or FTC. Please see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets and refer to other sections of the Drug Appendix for drug interaction information about each individual component of FDC tablets.

Major Toxicities

- *More common:* Headache, nausea
- *Less common (more severe):* Peripheral neuropathy, lipodystrophy/lipoatrophy
- *Rare:* Increased levels of liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

3TC is approved by the U.S. Food and Drug Administration (FDA) for the treatment of children aged ≥3 months.

Considerations for Use

The efficacy and toxicity of 3TC are equivalent to the efficacy and toxicity of FTC. The oral formulation of FTC has an advantage over the liquid formulation of 3TC because it can be given once daily at antiretroviral (ARV) initiation, whereas the liquid formulation of 3TC needs to be given twice daily at ARV initiation. When pill formulations of 3TC or FTC are used, they can be administered once daily.

Comparative Clinical Trials

Investigators studying the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort compared the efficacy of tenofovir disoproxil fumarate (TDF) plus FTC to TDF plus 3TC when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ART-naive patients.[2] The adjusted hazard ratio for the virologic failure of 3TC-containing regimens compared to FTC-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). These regimens had no difference in time to virologic suppression during the first 48 weeks of therapy or time to virologic failure after attaining suppression. In a Swiss cohort, Yang et al. found a potential difference in efficacy between FTC and 3TC; however, the difference disappeared after adjusting for pill burden. Current evidence suggests that FTC and 3TC have equivalent efficacy and toxicity in ARV-naive patients.[3]

Efficacy

3TC has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data have demonstrated the safety of 3TC and have shown that this drug is associated with clinical improvement and virologic response. It is commonly used in children with HIV as a component of a dual nucleoside reverse transcriptase inhibitor (NRTI) backbone.[4-12] In one study that evaluated the efficacy of NRTI background components, the combination of 3TC plus abacavir (ABC) was superior to zidovudine (ZDV) plus 3TC or ZDV plus ABC in achieving long-term virologic efficacy.[13]

Pharmacokinetics in Infants

Because of its safety profile and availability in a liquid formulation, 3TC has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.[9] A population pharmacokinetic (PK) analysis of infants who received 3TC affirms that adjusting the dose from 3TC 2 mg/kg to 3TC 4 mg/kg every 12 hours at age 4 weeks provides optimal 3TC exposure for infants with normal maturation of renal function.[14] For infants, the World Health Organization weight-band dosing (which is up to five times higher than the FDA-approved dose) results in greater plasma concentrations than the 3TC 2 mg/kg dose.[15] In HIV Prevention Trials Network (HPTN) 040, 3TC was administered as a component of a three-drug regimen to prevent perinatal transmission during the first 2 weeks of life. For 2 weeks, all infants weighing >2,000 g received 3TC 6 mg twice daily, and infants weighing ≤2,000 g received 3TC 4 mg twice daily. These doses resulted in 3TC exposure that was similar to the exposure seen in infants who received the standard twice-daily dosing schedule of 3TC 2 mg/kg per dose for neonates.[16]

Pharmacokinetics of Liquid versus Tablet Preparations

The PKs of 3TC have been studied after either single or repeat doses in 210 pediatric subjects. Pediatric subjects who received 3TC oral solution according to the recommended dose regimen achieved plasma concentrations of 3TC that were approximately 25% lower than those of adults with HIV who received the oral solution. Pediatric subjects who received 3TC tablets achieved plasma concentrations that were comparable to or slightly higher than those observed in adults who received tablets. In pediatric subjects, the relative bioavailability of 3TC oral solution is approximately 40% lower than the relative bioavailability of tablets that contain 3TC, despite no difference in the bioavailability of these two formulations among adults. The mechanisms for the diminished relative bioavailability of 3TC oral solution are unknown,[17] but results from a study in adults that compared the PKs of 3TC oral solution administered either alone or with increasing concentrations of sorbitol indicate that sorbitol decreases the total exposure of 3TC oral solution.[18] Sorbitol is a component of several ARV solutions, including ABC, as well as common over-the-counter medications that may be used in infants and young children; this may explain the PK discrepancy between the oral solution and tablet formulations. Modeling of PK data in pediatric patients suggests that increasing the oral solution dose to 3TC 5 mg/kg per dose twice daily or 3TC 10 mg/kg per dose once daily (with a maximum of 3TC 300 mg administered daily) in children aged ≥3 months would provide exposures similar to those seen in adult patients who received tablet formulations. However, modeling was done with PK data derived from studies that did not use 3TC liquid formulation, and so modeling may not predict exposures for 3TC oral solution, especially when used with liquid ABC. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** using a once-daily dose of 3TC until a child is aged ≥3 years. However, this new dosing schedule is now included in the 3TC package insert, even though no clinical data are available for patients who received both 3TC and sorbitol-containing medications.

Dosing Considerations—Once-Daily versus Twice-Daily Administration

The standard adult dose for 3TC is 300 mg once daily, but data are lacking on once-daily administration of 3TC in children. Population PK data indicate that once-daily dosing of 3TC 8 mg/kg leads to area under the curve over 24 hours ($AUC_{0–24h}$) values that are similar to those seen in patients taking 3TC 4 mg/kg twice daily, but minimum blood plasma concentration (C_{min}) values are significantly lower and maximum blood plasma concentration (C_{max}) values are significantly higher in children aged 1 year to 18 years.[19] Intensive PKs of once-daily versus twice-daily dosing of 3TC were evaluated in children with HIV aged 2 to 13 years in the PENTA (Paediatric European Network for Treatment of AIDS) 13 trial[4] and in children aged 3 months to 36 months in the PENTA 15 trial.[20] Both the PENTA 13 and PENTA 15 trials used a crossover design with doses of 3TC 8 mg/kg once daily or 3TC 4 mg/kg twice daily. $AUC_{0–24}$ and clearance values were similar between these two dosing schedules, and most children maintained an undetectable HIV RNA value after the switch. An ARROW (AntiRetroviral Research fOr Watoto) trial PK study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily 3TC also showed equivalent $AUC_{0–24h}$ and good clinical outcomes (defined by a low disease stage and a high CD4 T lymphocyte [CD4] cell count) after switching to once-daily 3TC. Median follow-up time during this study was 1.15 years.[21] The larger ARROW trial was a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of 3TC in >600 pediatric patients who had initiated therapy with twice-daily 3TC and who had been receiving therapy for ≥36 weeks. Median follow-up time during the study was 114 weeks. Rates of plasma HIV RNA suppression and adverse event profiles for once-daily 3TC were similar to (and statistically noninferior to) those of twice-daily 3TC.[22]

All four of the studies discussed above enrolled patients who had a low plasma HIV RNA or who were clinically stable on twice-daily 3TC before switching to once-daily dosing. Therefore, the Panel supports switching from twice-daily to once-daily dosing of 3TC in children aged ≥3 years who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 count. Clinicians should use a 10 mg/kg per dose of 3TC oral solution or a weight-based dose of 3TC tablets (neither exceeding 3TC 300 mg) as part of a once-daily regimen.[23] More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of 3TC can be used effectively as part of an initial ARV regimen in children.

3TC undergoes intracellular metabolism to reach its active form, 3TC triphosphate. In adolescents, the mean half-life of intracellular 3TC triphosphate (17.7 hours) is considerably longer than that of unphosphorylated 3TC in plasma (1.5–2 hours). Intracellular concentrations of 3TC triphosphate are equivalent whether 3TC is given once daily or twice daily in adults and adolescents. This supports a recommendation for once-daily 3TC dosing based on FDA recommendations.[24,25]

Considerations for Use

Weight-band dosing recommendations for 3TC have been developed for children weighing ≥3 kg and receiving either the 10-mg/mL oral solution or the 150-mg scored tablets.[26-28]

Both FTC and 3TC have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, see the Hepatitis B Virus section in the Pediatric Opportunistic Infection Guidelines.

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Tenofovir Alafenamide (TAF, Vemlidy)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Tablets: 25 mg[a]

Fixed-Dose (FDC) Combination Tablets

- [Biktarvy]
  - Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
  - Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg
- [Descovy]
  - Emtricitabine 200 mg/tenofovir alafenamide 25 mg
  - Emtricitabine 120 mg/tenofovir alafenamide 15 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg

When using FDC tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Biktarvy] Bictegravir (BIC)/Emtricitabine (FTC)/Tenofovir Alafenamide (TAF)

Neonate or Child (Aged <2 Years and Weighing <14 kg) Dose

- No data are currently available on the appropriate dose of Biktarvy in children aged <2 years and weighing <14 kg. Studies are currently being conducted to identify the appropriate dose for this age and weight group.

Child (aged ≥ 2 years), Adolescent, and Adult Dose

- One tablet once daily, with or without food.

Body Weight	Dose
≥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

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea
- Increased serum lipids

Special Instructions

- Measure serum creatinine before starting a TAF-containing regimen.
- Screen patients for hepatitis B virus (HBV) infection before initiating TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TAF.
- The FDA does not recommend using Genvoya with other ARV drugs, but this FDC tablet has been safely used with DRV.[1] Descovy can be safely used[2] with DRV or atazanavir in patients weighing ≥35 kg.

- The U.S. Food and Drug Administration (FDA) approved Biktarvy for use only in antiretroviral therapy (ART)-naive patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known mutations associated with resistance to the individual components of Biktarvy. Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommend the use of Biktarvy in patients with prior treatment failure who have virus with the M184V mutation. See the Bictegravir section for additional information.

[Descovy] FTC/TAF

Child, Adolescent, and Adult Dose

- One tablet once daily, with or without food.

Body Weight	Dose
≥14 kg to <25 kg	FTC 120 mg/TAF 15 mg, in combination with an integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). In this weight band, Descovy should not be used with protease inhibitors (PIs) that require a cytochrome P450 (CYP) 3A inhibitor (i.e., ritonavir [RTV] or cobicistat [COBI]).
≥25 kg to <35 kg	FTC 200 mg/TAF 25 mg, in combination with an INSTI or an NNRTI. In this weight band, Descovy should not be used with PIs that require a CYP3A inhibitor (i.e., RTV or COBI).
≥35 kg	FTC 200 mg/TAF 25 mg, in combination with an INSTI, NNRTI, or boosted PI.

[Genvoya] Elvitegravir (EVG)/COBI/FTC/TAF

Child (Aged ≥2 Years and Weighing 14 kg to <25 kg) Dose

- Data are currently limited on the appropriate dose of Genvoya in children aged ≥2 years to <6 years and weighing 14 kg to <25 kg. Studies are being conducted to identify the safety and efficacy of a low-dose Genvoya tablet. See the Elvitegravir section for details.

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily with food in ART-naive patients. This dose of Genvoya also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of

- **Do not use** Genvoya with EVG, COBI, tenofovir disoproxil fumarate, FTC, lamivudine, or PIs that are coformulated with COBI.
- When using Odefsey, patients must be able to take it with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal), because it contains RPV.

Metabolism/Elimination

TAF Dosing in Patients with Hepatic Impairment

- TAF-containing formulations do not require dose adjustment in patients with mild or moderate hepatic impairment, but they should not be used in patients with severe hepatic impairment because they have not been studied in that group.

TAF Dosing in Patients with Renal Impairment

- The TAF metabolite tenofovir is renally excreted.
- No dose adjustment of the TAF 25-mg tablet (Vemlidy)[a] is required in patients with estimated creatinine clearance (CrCl) ≥15 mL/min or in patients with estimated CrCl <15 mL/min (i.e., end-stage renal disease) who are receiving chronic hemodialysis. See the Vemlidy product label[3] for information on the use of the TAF 25-mg tablet in patients with estimated CrCl ≤15 mL/min.
- TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl <30 mL/min.

treatment failure, and no known mutations associated with resistance to the individual components of Genvoya. **[Odefsey] FTC/Rilpivirine (RPV)/TAF** *Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose* • One tablet once daily with a meal in ART-naive patients with HIV RNA ≤100,000 copies/mL. This dose of Odefsey also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known mutations associated with resistance to the individual components of Odefsey. **[Symtuza] Darunavir (DRV)/COBI/FTC/TAF** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose* • One tablet once daily with food in ART-naive patients. This dose of Symtuza also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known mutations associated with resistance to the individual components of Symtuza.	

[a] TAF 25-mg tablets (Vemlidy) are approved by the FDA for treatment of HBV. In certain circumstances, TAF 25-mg tablets (Vemlidy) might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Tenofovir alafenamide (TAF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein (P-gp) and the breast cancer resistance protein (BCRP). Drugs that strongly affect P-gp and BCRP activity may lead to changes in TAF absorption. P-gp inducers are expected to decrease TAF exposure, and P-gp inhibitors are expected to increase absorption and plasma concentrations of TAF.[2] A study of 98 healthy participants without HIV measured plasma TAF and tenofovir (TFV) exposures when TAF was administered with other antiretroviral (ARV) drugs. Coadministration of TAF with rilpivirine (RPV) and dolutegravir (DTG) did not change either TAF or TFV exposure. Coadministration of TAF with the P-gp and BCRP inhibitor cobicistat (COBI), or coadministration with atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r), increased both TAF and TFV exposures. Coadministration of TAF with darunavir/ritonavir (DRV/r) resulted in unchanged TAF area under the curve (AUC) and doubled TFV AUC. Coadministration of TAF with the P-gp and BCRP inducer efavirenz decreased TAF and TFV exposures.[4]
- Coadministration of TAF with rifamycins (rifabutin, rifampin, or rifapentine) **is not recommended.**[3,5]
- Genvoya contains elvitegravir (EVG) and COBI, in addition to TAF (see the Elvitegravir and Cobicistat sections for details). EVG is metabolized predominantly by cytochrome P450 (CYP) 3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, and by oxidative

metabolism pathways. EVG is a modest inducer of CYP2C9. COBI is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, COBI inhibits the adenosine triphosphate-dependent transporters BCRP and P-gp and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions when using both EVG and COBI.

- *Absorption:* Administering EVG and bictegravir (BIC) concurrently with antacids or supplements that contain iron, calcium, aluminum and/or magnesium lowers plasma concentrations of these ARV drugs (see the Elvitegravir and Bictegravir sections for details).
- Odefsey contains RPV, which is a CYP3A substrate, and requires dose adjustments when administered with CYP3A-modulating medications.
- Before Genvoya, Odefsey, Descovy, Biktarvy, or Symtuza is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion (e.g., acyclovir, ganciclovir, high-dose nonsteroidal anti-inflammatory drugs) could reduce clearance of the TAF metabolite TFV or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Genvoya.
- *Protease inhibitors:* Genvoya should not be administered concurrently with products or regimens that contain ritonavir (RTV), because COBI and RTV have similar effects on CYP3A metabolism.

Major Toxicities

- *More common:* Nausea, diarrhea, headache. Greater weight gain has been reported with the use of TAF than with tenofovir disoproxil fumarate (TDF) in adults and children[6] (see Table 15h. Lipodystrophies and Weight Gain for details).
- *Less common (more severe):* Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs).

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

TAF is available as a component of several fixed-dose combination (FDC) tablets. These FDC tablets are listed in Appendix A, Table 1 and Appendix A, Table 2.

Descovy, an FDC tablet that contains FTC and TAF (FTC/TAF), is approved by the U.S. Food and Drug Administration (FDA) for use in children who weigh ≥14 kg to <25 kg at a dose of FTC 120 mg/TAF 15 mg and for children who weigh ≥25 kg to <35 kg at a dose of FTC 200 mg/TAF 25 mg when used as part of an ARV regimen that does not include a boosted protease inhibitor (PI). Descovy is approved by the FDA for use in children who weigh ≥35 kg at a dose of FTC 200 mg/TAF 25 mg when used in combination with any ARV drugs, including RTV-boosted or

COBI-boosted PIs. Odefsey, an FDC tablet that contains FTC, RPV, and TAF (FTC/RPV/TAF), is approved by the FDA[7] for use in children who weigh ≥35 kg. Genvoya, an FDC tablet that contains EVG, COBI, FTC, and TAF (EVG/c/FTC/TAF), is approved by the FDA for use in children who weigh ≥25 kg when used without other ARV drugs[8] (see Table A below). BIC is available only as part of the FDC tablet Biktarvy, which contains BIC, FTC, and TAF (BIC/FTC/TAF). Biktarvy is approved by the FDA[9,10] for use in children or adolescents with body weight ≥14 kg to <25 kg at a dose of BIC 30 mg/FTC 120 mg/TAF 15 mg and for children, adolescents, and adults with body weight ≥25 kg at a dose of BIC 50 mg/FTC 200 mg/TAF 25 mg.[10,11] Symtuza, an FDC tablet that contains DRV, COBI, FTC, and TAF (DRV/c/FTC/TAF) is approved by the FDA[12] for use in children and adolescents who weigh ≥40 kg.

TAF has antiviral activity and efficacy against hepatitis B virus (HBV). Testing for HBV should be performed prior to starting treatment with TAF. If HBV is found, rebound of clinical hepatitis could occur when TAF is stopped. For more information about hepatitis rebound in patients with HBV/HIV coinfection, see the Hepatitis B Virus section of the Pediatric Opportunistic Infection Guidelines. TAF alone (as Vemlidy) is approved by the FDA for use in persons aged ≥8 years, but it is approved only for treating HBV, not HIV.

Formulations

TAF-containing pills are smaller than their TDF-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills (see Appendix A, Table 2). EVG/c/FTC/TAF contains TAF 10 mg, whereas FTC/TAF and FTC/RPV/TAF contain TAF 25 mg. BIC/FTC/TAF is available in two strengths: one containing TAF 15 mg for children aged ≥2 years and weighing <25 kg and the other containing TAF 25 mg for persons weighing ≥25 kg. COBI boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, in persons weighing ≥25 kg, administration of EVG/c/FTC/TAF, which contains TAF 10 mg and COBI, achieves TFV-DP systemic exposure that is similar to the exposure achieved by FTC/RPV/TAF or BIC/FTC/TAF containing TAF 25 mg but no COBI.

Table A. U.S. Food and Drug Administration–Approved Tenofovir Alafenamide-Containing Formulations

Drug	Contains	Dose of TAF	Minimum Age	Minimum Body Weight or Weight Range	Comment
Vemlidy	TAF	25 mg	18 years	N/A	Approved for HBV treatment only.
Descovy	FTC/TAF	15 mg	N/A	≥14 kg to <25 kg	Use with an INSTI or NNRTI, but **not** with a boosted PI.
	FTC/TAF	25 mg	N/A	≥25 kg	
	FTC/TAF	25 mg	N/A	35 kg	Use with any ARV drugs, including a boosted PI.
Odefsey	FTC/RPV/TAF	25 mg	12 years	35 kg	**Generally not to be used with other ARV drugs.**[a]
Genvoya	EVG/c/FTC/TAF	10 mg	N/A	25 kg	TAF dose is lower due to the COBI boosting. **Generally not to be used with other ARV drugs.**[a]
Symtuza	DRV/c/FTC/TAF	10 mg	N/A	40 kg	TAF dose is lower due to the COBI boosting. **Generally not to be used with other ARV drugs.**[a]
Biktarvy	BIC/FTC/TAF	15 mg	N/A	≥14 kg to <25 kg	**Generally not to be used with other ARV drugs.**[a]
	BIC/FTC/TAF	25 mg	N/A	≥25 kg	

[a] Consult a specialist in HIV care before using these fixed-dose combination tablets with other ARV agents.

Key: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide

Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate

Both TDF and TAF are prodrugs of the NRTI TFV. After oral administration, TDF is well absorbed[13,14] and is so rapidly metabolized to TFV that TDF itself cannot be measured in blood (even when plasma is sampled within 5 minutes of administration).[15] TFV is the main compound that is measurable in plasma after TDF administration. From the bloodstream, TFV enters cells and is phosphorylated to the active agent TFV-DP.

TAF also has good oral bioavailability.[16,17] Within the enterocyte and liver, TAF is not metabolized to TFV as quickly as TDF, so the plasma TFV concentration is much lower with administration of TAF than with TDF, and the main component in plasma is the prodrug itself, TAF.[18] Once inside the cell, TAF is hydrolyzed to TFV,[19,20] and then TFV-DP is produced by the same mechanism as for TDF. Relative to TDF, TAF more effectively delivers TFV to cells throughout the body.[16] Therefore, a much lower dose of TAF results in intracellular concentrations of TFV-DP that are higher than the concentrations seen after TDF administration (see Table B below). Additionally, the half-life of TFV-DP in peripheral blood mononuclear cells is longer for TAF (2.9 days, 95% confidence interval [CI], 1.5–5.5) than for TDF (2.1 days, 95% CI, 1.5–2.9).[21]

The key pharmacokinetic (PK) difference between TDF and TAF is that TDF results in higher plasma TFV concentrations than TAF, but when administered at FDA-approved doses, both drugs produce high, therapeutically effective intracellular TFV-DP concentrations.[18,22] Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy that is equivalent to the antiviral efficacy of TDF. However, the toxicities that are specifically related to high plasma TFV concentrations should not occur when using TAF. High plasma TFV concentration has been linked to TDF-related endocrine disruption that is associated with low bone mineral density (BMD).[23] High plasma TFV concentration also has been closely associated with both glomerular[23-25] and proximal tubular[26] renal toxicity.

Table B. Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV: Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate

Parameter	TAF 25 mg (n = 8)	TDF 300 mg (n = 6)
Plasma TFV AUC_{tau} (ng·h/mL)	267.7 (26.7)	1,918.0 (39.4)
Plasma TFV C_{max} (ng/mL)	15.7 (22.1)	252.1 (36.6)
Plasma TFV C_{tau} (ng/mL)	9.2 (26.1)	38.7 (44.7)
PBMC TFV-DP AUC_{tau} (μM·h)	21.4 (76.9)	3.0 (119.6)

Note: The mean age of participants was 38 years, with a range of 20 to 57 years. Data presented are mean (% coefficient of variation) .

Source: Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr*. 2013;63(4):449-455. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23807155.

Key: AUC = area under the curve; AUC_{tau} = AUC for dosing interval (i.e., 24 hours); C_{max} = peak concentration; C_{tau} = concentration at the end of a dosing interval (i.e., at 24 hours, the trough concentration); PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate

Tenofovir Alafenamide Efficacy in Clinical Trials in Adults

In adults, TAF is noninferior to TDF in its ability to control viral load over 48 to 96 weeks when used in combination with EVG, COBI, and FTC[27-30]; with FTC and RPV[31]; with DRV, COBI, and FTC[32-34]; and when TAF and FTC are administered in combination with other ARV drugs.[35] In a switch study of adults who were virologically suppressed on a three-drug regimen that included abacavir (ABC), FTC/TAF was noninferior to a regimen of lamivudine plus ABC plus a third ARV drug over 48 weeks. No differences occurred in BMD or the frequency of renal glomerular toxicities or renal tubular toxicities between these groups, but the TAF group showed a decline in high-density lipoprotein (HDL) cholesterol levels, whereas the ABC group had an increase in HDL cholesterol levels[36] (−2 mg/dL vs. +2 mg/dL, respectively; $P = 0.0003$). Viral load suppression was attained in about 90% of study participants when TAF was given as part of the coformulated BIC/FTC/TAF.[37-39]

Tenofovir Alafenamide Efficacy in Clinical Trials in Adolescents and Children

The combination of EVG, COBI, FTC, and TAF has been shown to have similar efficacy when used in adults and two groups of children: those weighing ≥35 kg and aged ≥12 years[40] and those weighing ≥25 kg and aged ≥6 years[41] (see the Elvitegravir section for details). In a switch study, treatment with BIC/FTC/TAF resulted in viral load suppression at 48 weeks in 49 of 50 (98%) children aged 6 years to <12 years, and in 50 of 50 (100%) children aged 12 years to <18 years[9] (see the Bictegravir section for details).

Pharmacokinetics

Drug Exposure and Virologic Response

Virologic suppression in people who are taking TAF or TDF is most closely related to intracellular TFV-DP concentrations. In adults, TAF generates peripheral blood mononuclear cell TFV-DP concentrations that are twofold[22] to sevenfold higher than those generated with TDF, at clinically meaningful doses.[18,21,27] Higher TFV-DP concentrations result in a stronger antiviral potency[18] and a higher barrier to resistance.[42,43] Therefore, because TAF administration leads to higher intracellular TFV-DP concentrations than TDF, TAF may be more effective against NRTI-resistant virus than TDF. The mean TFV-DP concentration is higher in youth aged 12 to 18 years than in adults: 221.8 fmol/million cells (with a coefficient of variation [CV] of 94.4%) versus 120.8 fmol/million cells (CV 91.4%), respectively.[40]

Drug Exposure and Safety: All Age Groups

FTC/TAF can be safely combined with DTG or raltegravir without concern for drug interactions. FTC and TAF also have been safely combined with BIC in the FDC tablet Biktarvy.

When FTC/TAF, which contains TAF 25 mg, is combined with boosted ATV, DRV, or LPV, the P-gp inhibitors COBI or RTV increase the TAF exposure to higher concentrations than those seen with the use of EVG/c/FTC/TAF, which contains TAF 10 mg. However, the plasma TFV concentrations seen with the use of EVG/c/FTC/TAF or TAF plus DRV/r or DRV/c are still much lower than those seen with the use of Stribild, an FDC tablet that contains EVG, COBI, FTC, and TDF (see Table C below).

Table C. Plasma Tenofovir Alafenamide and Plasma Tenofovir Exposures When Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate Are Used with Boosted Antiretroviral Drugs

Regimen	TAF AUC[a]	**TAF AUC Ratio** TAF AUC of TAF-Containing Regimen/TAF AUC of Genvoya (Adult Exposure)	TFV AUC[a]	**TFV AUC Ratio** TFV AUC of TAF-Containing Regimen/TFV AUC of Stribild (Adult Exposure)
Adult				
Stribild (EVG/c/FTC/TDF 300 mg)	N/A	N/A	4,400	1.00
Genvoya (EVG/c/FTC/TAF 10 mg)	210	1.0	290	0.07
DRV/r plus TAF 25 mg[b]	196	0.93	259	0.06
DRV/c plus TAF 25 mg	239	1.1	935	0.21
Pediatric				
Stribild (EVG/c/FTC/TDF 300 mg) for ages 12–18 years	N/A	N/A	6,028	1.37
Genvoya (EVG/c/FTC/TAF 10 mg) for ages 12–18 years	200	0.95	290	0.07
Genvoya (EVG/c/FTC/TAF 10 mg) for ages 6–12 years	330	1.6	440	0.10

[a] AUC: ng·h/mL

[b] Values for this row do not come from observed data. These values were predicted based on data from studies that used TAF 10 mg. The AUC values predicted for TAF 25 mg were obtained by multiplying the TAF 10 mg AUC by 2.5 for both TAF and TFV AUC.

Source: Table modified from U.S. Food and Drug Administration Summary Review of TAF and from the TAF clinical pharmacology review using data from the Stribild product label and Genvoya product label.

Key: AUC = area under the curve; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

The clinical trials in adults that have shown the safety of FTC plus TAF administered with ATV/r or DRV/r have used FTC 200 mg/TAF 10 mg, a formulation that is not available in the United States.[44] The FDA states that when FTC 200 mg/TAF 25 mg is combined with boosted ATV, DRV, or LPV in adults, "no clinically significant drug interactions have been observed or are expected."[2] The combination of FTC 200 mg/TAF 25 mg is approved by the FDA for use in adults, independent of the accompanying ARV drugs (which may include a boosted PI or an integrase strand transfer inhibitor [INSTI]).[2] Moreover, in Trial GS-US-299-0102 (NCT01565850) a Phase 2b trial in adults that compared a regimen of DRV/c plus FTC/TAF 10 mg to a regimen of DRV/c plus FTC/TDF, virologic outcomes at Week 48 were worse for participants in the TAF 10-mg arm than in the TDF arm.[45] Hence, FTC/TAF 25 mg was recommended for approval instead of FTC/TAF 10 mg.[45] This is not the case in Canada or Europe where FTC is combined with TAF 10 mg in an FDC for use in combination with boosted PIs.

Drug Exposure and Safety: Aged 12 to 18 Years and Weighing ≥35 kg

A study of FTC/TAF in 18 children and adolescents (aged 12 years to 18 years and weighing ≥35 kg) was performed using FTC 200 mg/TAF 10 mg plus a boosted third ARV drug or FTC 200 mg/TAF

25 mg with an unboosted third ARV drug. The results of this study showed TAF exposures in children and adolescents that were like those seen in adults. TAF was well tolerated and efficacious during the 24 weeks of study. Asymptomatic Grade 3 or 4 elevations in amylase levels were noted in 5 of 28 participants (18%), and Grade 3 or 4 elevations in fasting low-density-lipoprotein (LDL) levels were noted in 2 of 28 participants (7%).[46]

Studies of EVG/c/FTC/TAF in children aged 12 years to 18 years and weighing ≥35 kg showed that TAF and TFV exposures were like those found in adults (see Table C above), and that the drug combination was well tolerated and efficacious over 48 weeks of study.[40] Because these TAF and TFV exposures were similar to those seen in adults, FTC 200 mg/TAF 25 mg was also approved by the FDA for use in this age and weight group, independent of the accompanying ARV drugs in the regimen (which may include a boosted PI or an INSTI).[2]

The formulation of Biktarvy, which contains BIC 50 mg/FTC 200 mg/TAF 25 mg, was administered to 50 children aged 6 years to <12 years and weighing ≥25 kg and 50 children and adolescents aged 12 years to <18 years and weighing ≥35 kg who had had viral loads <50 copies/mL for at least 6 months. The drug was well tolerated. All 50 participants in the study[9] had viral loads <50 copies/mL at Week 24, and 49 participants had viral loads <50 copies/mL at Week 48 (see the Bictegravir section for details).

Drug Exposure and Safety: Aged 6 Years to <12 Years and Weighing 25 kg to <35 kg

Studies of EVG/c/FTC/TAF in children aged 6 years to <12 years who weighed ≥25 kg showed that TAF and TFV exposures were somewhat higher than those found in adults (see Table C above), but the drug combination was well tolerated and efficacious over 24 weeks of study.[41,47] This led to FDA approval of EVG/c/FTC/TAF for use in children aged ≥6 years and weighing ≥25 kg.[8] Follow-up to 96 weeks in a small number of participants showed no change from baseline in the median spine BMD z-score, but there was a decline in the median total body BMD z-score, and a possible decline in the median estimated glomerular filtration rate.[48]

Because INSTIs do not increase TAF concentrations, regimens that include FTC/TAF 25 mg plus an INSTI are expected to result in safe drug exposures that are like those seen with coformulated EVG/c/FTC/TAF 10 mg. This led the FDA to approve FTC/TAF 25 mg for use in children aged ≥6 years and weighing ≥25 kg when used in combination with other ARV drugs that do not include a boosted PI.[2]

Because boosted ATV, DRV, or LPV increase TAF exposure to concentrations that are higher than those seen with use of EVG/c/FTC/TAF, and because no data exist on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with COBI-boosted or RTV-boosted PIs in children weighing between 25 kg and <35 kg cannot be assured. Therefore, FDA approval for FTC/TAF used in combination with boosted PIs is limited to children weighing ≥35 kg (see Table A above).[2]

Drug Exposure and Safety: Aged ≥2 Years and Weighing ≥14 kg to <25 kg

Biktarvy tablets consisting of BIC 30 mg/FTC 120 mg/TAF 15 mg were administered to children aged ≥2 years weighing 14 kg to <25 kg and who had viral loads <50 copies/mL on stable ART. At 24 weeks, the median change in CD4 T lymphocyte (CD4) cell count was −100 cells/mm^3, and the change in CD4 percentage was +0.5%. HIV RNA at <50 copies/mL was maintained in 20 of the 22 participants at 24 weeks[49] (see the Bictegravir section for details).

Dosing: Crushing Emtricitabine/Tenofovir Alafenamide Tablets

Viral load suppression was reported in one adult patient with HIV who received crushed FTC/TAF tablets plus crushed DTG tablets. The crushed tablets were mixed with water and administered via a gastrostomy tube. Each dose was followed by a can of a nutritional supplement. No PK parameters were measured.[50] In adults without HIV, the PKs of crushed DRV/c/FTC/TAF tablets showed decreased TAF bioavailability compared to whole tablets. The clinical implications of these findings are unclear.[51]

Toxicity

Bone

TAF causes bone toxicity less frequently than TDF.[27-29,32-35,52,53] For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/c/FTC/TAF had a smaller decrease in BMD at the spine (mean change −1.30% vs. −2.86%; $P < 0.0001$) and hip (−0.66% vs. −2.95%; $P < 0.0001$) at 48 weeks than those given EVG/c/FTC/TDF.[27] These differences were maintained until 96 weeks.[30] The clinical importance of these changes in BMD is unclear.

Renal

Studies in adolescents aged 12 to 17 years[40] and adults[27-29,32,33,35] show that TAF is less frequently associated with glomerular and renal tubular damage than TDF.[54] For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/c/FTC/TAF had a smaller mean increase in serum creatinine (0.08 mg/dL vs. 0.12 mg/dL; $P < 0.0001$) than those given EVC/c/FTC/TDF, and a smaller percent change from baseline in urine protein to creatinine ratio (median % change −3% vs. +20%; $P < 0.0001$) at 48 weeks.[27] These differences persisted until 96 weeks of follow up.[30] Safety of EVG/c/FTC/TAF has been demonstrated in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.[55] TAF may require less intense renal safety monitoring than TDF, but more experience with the drug in broad clinical practice will be needed before a specific recommendation can be made.

Lipids

In treatment-naive adults who were evaluated after 48 weeks of therapy, initiation of EVG/c/FTC/TAF was associated with increases in serum lipids that were greater than those observed with the initiation of EVG/c/FTC/TDF, with a mean increase in total cholesterol levels of 31 mg/dL versus 23 mg/dL, and a mean increase in LDL cholesterol levels of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents who were treated with EVG/c/FTC/TAF, the following median changes from baseline occurred at Weeks 24 and 36: Fasting total cholesterol levels increased 26 mg/dL and 36 mg/dL, respectively; fasting direct LDL levels increased 10 mg/dL and 17 mg/dL, respectively; and fasting triglycerides increased 14 mg/dL and 19 mg/dL, respectively.[56] Similar TAF-related increases in total cholesterol levels and LDL cholesterol levels have been found when TAF is administered with other combinations of ARV drugs.[33] Monitoring serum lipids while the patient is taking TAF-containing FDC tablets is warranted, given these data (see Table 15b. Dyslipidemia for details).

Weight Gain

Observational data are limited and no randomized controlled trials have examined TAF-associated weight gain in children. In adults, greater weight gain has been reported with the use of TAF than with the use of TDF[57-63] (see Table 15h. Lipodystrophies and Weight Gain for details). Although weight gain at ART initiation might represent a "return to health," [63] patients initiating treatment with TAF had larger increases in weight than those initiating treatment with TDF[58,59]; increases in weight and BMI have been observed in ARV switch studies, as well.[60,63,64] In adults, the effect may be greatest in Black females,[59,63] especially if administered in combination with INSTIs.[59,61] A study in adult women showed increased BMI with the switch to either an INSTI or TAF, but these BMI increases were only seen in persons with BMI <30 kg/m^2 at baseline.[57]

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Tenofovir Disoproxil Fumarate (TDF, Viread)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Oral Powder: 40 mg per 1 g of oral powder (one level scoop, measured with supplied dosing scoop, equals 1 g oral powder)
Tablets: 150 mg, 200 mg, 250 mg, and 300 mg
Fixed-Dose Combination (FDC) Tablets
• [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
• [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
• [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
• [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
• [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
• [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
• [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
• [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
• [Truvada tablet]
    ○ Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
    ○ Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg
    ○ Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg
    ○ Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg
When using FDC tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.
For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Neonate and Infant Dose • Tenofovir disoproxil fumarate (TDF) has not been approved by the U.S. Food and Drug Administration (FDA) or recommended for use in neonates or infants aged <2 years. **Child (Aged ≥2 Years to <12 Years) and Weighing ≥10 kg Dose[a]** • TDF 8 mg/kg per dose once daily	• Asthenia, headache, diarrhea, nausea, vomiting, flatulence • Glomerular and proximal renal tubular dysfunction • Decreased bone mineral density[a]

TDF Oral Powder Dosing Table

Body Weight	**TDF Oral Powder** Once-Daily Scoops of Powder
10 kg to <12 kg	2 scoops (80 mg)
12 kg to <14 kg	2.5 scoops (100 mg)
14 kg to <17 kg	3 scoops (120 mg)
17 kg to <19 kg	3.5 scoops (140 mg)
19 kg to <22 kg	4 scoops (160 mg)
22 kg to <24 kg	4.5 scoops (180 mg)
24 kg to <27 kg	5 scoops (200 mg)
27 kg to <29 kg	5.5 scoops (220 mg)
29 kg to <32 kg	6 scoops (240 mg)
32 kg to <34 kg	6.5 scoops (260 mg)
34 kg to <35 kg	7 scoops (280 mg)
≥35 kg	7.5 scoops (300 mg)

Body Weight	**TDF Tablet** Once Daily
17 kg to <22 kg	150 mg
22 kg to <28 kg	200 mg
28 kg to <35 kg	250 mg
≥35 kg	300 mg

Child and Adolescent (Weighing ≥35 kg)[a] and Adult Dose

- TDF 300 mg once daily

[Atripla and Generic] Efavirenz/Emtricitabine/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

Special Instructions

- TDF oral powder formulation is available for patients who are unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: one level scoop = 1 g powder = TDF 40 mg.
- Mix TDF oral powder with 2 to 4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with liquid. The powder may float on the top even after vigorous stirring.
- Although TDF can be administered without food, food requirements vary depending on the other ARV drugs contained in an FDC tablet. Food requirements are listed with dosing recommendations and in Appendix A, Table 2.
- Measure serum creatinine and perform a urine dipstick test for protein and glucose before starting a TDF-containing regimen. Serum creatinine should be monitored, and urine should be tested for protein and glucose at intervals during continued therapy (see Table 15i. Nephrotoxic Effects). Measure serum phosphate if there is clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before using TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TDF.
- Tenofovir alafenamide (TAF) is associated with less bone and renal toxicity than TDF, but it has equal antiviral efficacy. **Do not use TAF and TDF together.** Consider switching from TDF to TAF in appropriate clinical settings.

	Metabolism/Elimination
[Cimduo] Lamivudine/TDF *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* • One tablet once daily **[Complera] Emtricitabine/Rilpivirine/TDF** *Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose* • One tablet once daily in antiretroviral therapy (ART)-naive adults with baseline HIV RNA ≤100,000 copies/mL. This dose of Complera also can be used in virologically suppressed (HIV RNA <50 copies/mL) adults who are currently on their first or second regimen and who have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs. • Administer with a meal of ≥500 calories. **[Delstrigo] Doravirine/Lamivudine/TDF** *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* One tablet once daily in ART-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known mutations associated with resistance to the individual components of Delstrigo **[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF** *Adolescent (Weighing >35 kg with a Sexual Maturity Rating [SMR] of 4 or 5) and Adult Dose* • One tablet once daily in ART-naive adults. This dose of Stribild also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known mutations associated with resistance to the individual components of Stribild. • Administer with food. **[Symfi] Efavirenz 600 mg/Lamivudine/TDF** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose* • One tablet once daily • Take on an empty stomach. **[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF** *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* • One tablet once daily • Take on an empty stomach. • Symfi Lo has not been studied in children (SMR 1 to 3), and major inter-individual variability in efavirenz (EFV)	**TDF Dosing in Patients with Hepatic Impairment** • No change in TDF dosing is required for patients with hepatic impairment. • Stribild should not be used in patients with severe hepatic impairment. • Atripla, Symfi, and Symfi Lo should be used with caution in patients with hepatic impairment; Symfi and Symfi Lo are not recommended for use in moderate or severe hepatic impairment. **TDF Dosing in Patients with Renal Insufficiency** • The tenofovir metabolite of TDF is renally excreted. • The dose of TDF should be decreased in patients with impaired renal function (creatinine clearance [CrCl] <50 mL/min). Consult the manufacturer's prescribing information for directions on how to adjust the dose in accordance with CrCl. • The FDCs Atripla, Cimduo, Complera, Delstrigo, Symfi, Symfi Lo, or Temixys should not be used in patients with CrCl <50 mL/min or in patients who require dialysis. • The FDC Truvada should not be used in patients with CrCl <30 mL/min or in patients who require dialysis. • The FDC Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.

plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs of 1 to 3 who weigh ≥40 kg. Some members of The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV suggest therapeutic drug monitoring when Symfi Lo is used in pediatric patients weighing ≥40 kg. See the Efavirenz section for more information. **[Temixys] Lamivudine/TDF** *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* • One tablet once daily **[Truvada] Emtricitabine/TDF (FTC/TDF)** *Child, Adolescent, and Adult Dose* **Truvada Dosing Table**	

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	One FTC 100 mg/TDF 150 mg tablet
22 kg to <28 kg	One FTC 133 mg/TDF 200 mg tablet
28 kg to <35 kg	One FTC 167 mg/TDF 250 mg tablet
≥35 kg and adults	One FTC 200 mg/TDF 300 mg tablet

[a] See the text for a discussion of the concerns about decreased bone mineral density in patients who are receiving TDF, especially in prepubertal patients and those in early puberty (SMR 1 or 2).

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Tenofovir disoproxil fumarate (TDF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein and breast cancer resistance protein. When TDF is coadministered with inhibitors of these transporters, an increase in TDF absorption may be observed, with the potential for enhanced TDF toxicity.[1]
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of plasma tenofovir (TFV). Avoid frequent or long-term use of nonsteroidal anti-inflammatory drugs in patients who are taking TDF.
- *Other nucleoside reverse transcriptase inhibitors:* Didanosine (ddI) serum concentrations increase when this drug is coadministered with TDF, and this combination **should not be used** because of the increased risk of ddI toxicity.
- *Protease inhibitors (PIs):* Atazanavir (ATV) without ritonavir (RTV) **should not be coadministered** with TDF, because TDF decreases ATV plasma concentrations. The

combination of ATV/r, darunavir/r, and lopinavir/r increases plasma TFV concentrations and increases the risk of TDF-associated toxicity.[1,2]

- *Absorption:* Administering elvitegravir (EVG) concurrently with antacids and supplements that contain iron, calcium, aluminum, and/or magnesium lowers plasma concentrations of EVG. If using Stribild, see the Elvitegravir section of Appendix A: Pediatric Antiretroviral Drug Information for additional information.

Major Toxicities

- *More common:* Nausea, diarrhea, vomiting, flatulence
- *Less common (more severe):* TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF. Renal toxicity—including increased serum creatinine, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreased serum phosphate—has been observed. Patients at increased risk of renal glomerular or tubular dysfunction should be closely monitored. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

TDF has been approved by the U.S. Food and Drug Administration (FDA) for use in children aged ≥2 years and weighing ≥10 kg when used as a component of antiretroviral therapy (ART). TDF is available as a component of fixed-dose combination tablets (see Appendix A, Table 2).

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is approved by the FDA for HBV treatment in children aged ≥2 years and weighing ≥10 kg. For a comprehensive review of this topic, see the Hepatitis B Virus section in the Pediatric Opportunistic Infection Guidelines.

Efficacy in Clinical Trials in Adults Compared with Children and Adolescents

The standard adult dose that was approved by the FDA for adults and children aged ≥12 years and weighing ≥35 kg is TDF 300 mg once daily. For children aged 2 to 12 years, the FDA-approved dose is TDF 8 mg/kg per dose administered once daily, which closely approximates the dose of TDF 208 mg/m^2 per dose used in early studies in children.[3]

In adults, the recommended once-daily dose of TDF 300 mg is highly effective when used in combination with other antiretroviral (ARV) drugs.[4-11] The FDA approved Cimduo and Temixys (both of which contain lamivudine [3TC] 300 mg/TDF 300 mg) and Symfi (efavirenz [EFV] 600 mg/3TC 300 mg/TDF 300 mg) based on results of prior clinical trials.[5,12] FDA approval of Symfi Lo (EFV 400 mg/3TC 300 mg/TDF 300 mg) was based on a study that compared the use of

EFV 400 mg with the use of EFV 600 mg, each administered with emtricitabine 200 mg and TDF 300 mg, in 630 ART-naive adults.[13] See the Efavirenz section for a detailed discussion of this study.

In children, the published efficacy data for TDF-containing ARV combinations are mixed, but potency equal to that in adults has been seen in pediatric patients aged 3 to 18 years with susceptible virus. In children aged 2 years to <12 years, TDF 8 mg/kg per dose once daily was noninferior to twice-daily zidovudine-containing ART or stavudine-containing ART over 48 weeks of randomized treatment.[14,15] Virologic success is lower in treatment-experienced patients with extensive multiclass drug resistance.[16-18]

Pharmacokinetics

Relationship of Drug Exposure to Virologic Response

Virologic suppression is most closely related to intracellular tenofovir diphosphate (TFV-DP) concentrations and, for TDF, intracellular TFV-DP is linked to plasma TFV concentration.[19] A modeling study suggests that children and adolescents who are treated with TDF may have higher intracellular TFV-DP concentrations than adults,[20] even though plasma TFV concentrations are lower in children and adolescents, because weight-adjusted renal clearance of TFV is higher in children than in adults.[3,21,22]

Formulations

Special Considerations

The taste-masked granules that make up the TDF oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed with a vehicle, TDF should be administered promptly because its taste becomes bitter when it is allowed to sit for too long.

Toxicity

Bone Toxicity

TDF administration is associated with decreased BMD in both adults[23,24] and children.[15,25-27] When treated with TDF, younger children with sexual maturity ratings (SMRs) of 1 and 2 may be at a higher risk of decreased BMD than children with more advanced pubertal development (i.e., SMRs ≥3).[21] Discontinuation of TDF results in partial or complete recovery of BMD.[25,28]

In the study that led to FDA approval of TDF in adolescents aged ≥12 years and weighing ≥35 kg, 6 of 33 participants (18%) in the TDF arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks, whereas only 1 of 33 participants (3%) in the placebo arm experienced this decline.[16]

TDF administration disrupts vitamin D metabolism,[29,30] and the decrease in BMD associated with TDF initiation was attenuated in adults with coadministration of high doses of vitamin D3 (4,000 International Units [IU] daily) and calcium carbonate (1,000 mg daily) for the first 48 weeks of TDF treatment.[31] During chronic TDF administration, youth with HIV who received vitamin D3 supplements (50,000 IU once monthly) had decreased serum parathyroid hormone levels and increased lumbar spine BMD compared with study participants who were not treated with high doses of vitamin D3.[29,32] The serum 25-hydroxy vitamin D concentration was 37 ng/mL in the group with improved BMD. Similar improvements in BMD were seen in youth with HIV who were treated with an ARV regimen that included TDF and who received vitamin D3 2,000 IU or 4,000 IU daily.[33] Measurement of plasma vitamin D concentration is recommended for patients who are being treated with an ARV regimen that includes TDF, and vitamin D supplementation is recommended for those with vitamin D deficiency (see Table 15j. Osteopenia and Osteoporosis).

High concentrations of the TDF metabolite plasma TFV have been associated with TDF-related endocrine disruption and low BMD.[34] Plasma TFV concentrations are higher when TDF is coadministered with boosted PIs.[1] Tenofovir alafenamide (TAF), which is associated with lower plasma TFV concentrations than TDF, has less effect on parathyroid hormone levels[35] and causes less decline in BMD than TDF. See the Tenofovir Alafenamide section for more information. Consider switching from TDF to TAF or avoiding coadministration of TDF with boosted PIs in patients for whom loss of BMD is a concern.

Monitoring Potential Bone Toxicity

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend routine dual-energy X-ray absorptiometry (DXA) monitoring for children or adolescents who are being treated with TDF (see Table 15j. Osteopenia and Osteoporosis).

TDF has been shown to be effective, and it can be administered once daily; however, the use of TDF has been associated with a risk of BMD loss. Because childhood and early adolescence are important periods of rapid bone accrual, and because children with perinatally acquired HIV are at risk for low peak bone mass,[36,37] the Panel favors the use of abacavir or TAF over TDF in children with SMRs 1 to 3.

Renal Toxicity

New-onset renal impairment and worsening renal impairment have been reported in adults[38] and children[39,40] receiving TDF. In one study, renal toxicity led to discontinuation of TDF in 6 of 159 (3.7%) children with HIV who were treated with TDF.[18] Although TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.[38,39] Irreversible renal failure is quite rare, but cases have been reported.[41]

The main target of TDF nephrotoxicity is the renal proximal tubule.[39] Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.[42,43]

Subclinical renal tubular damage is more common than clinically apparent renal tubular injury. Increased urinary beta-2 microglobulin was identified in 12 of 44 children (27%) who were treated with TDF and in 2 of 48 children (4%) who were not treated with TDF.[44] The risks of TDF-associated proteinuria and chronic kidney disease increase with the duration of treatment.[45,46] Of 89 participants aged 2 to 12 years who received TDF in Gilead Study 352 (where participants had a median drug exposure of 104 weeks), four participants were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.[14] In adults, renal dysfunction is more common when TDF is used in patients with older age or a pre-existing renal disease[47]; in children, renal dysfunction may be more common when TDF is used with boosted PIs than with non-nucleoside reverse transcriptase inhibitors.[48]

Plasma TFV is the TDF metabolite most closely associated with both glomerular[34,49] and proximal tubular[50] toxicity. As previously noted, plasma TFV concentrations are higher when TDF is coadministered with boosted PIs.[1] TAF, which generates lower plasma TFV concentrations than TDF, is associated with a lower risk of renal toxicity than TDF[51] (see Tenofovir Alafenamide).

Monitoring Potential Renal Toxicity

Because TDF has the potential to decrease creatinine clearance and cause renal tubular dysfunction, the Panel recommends measuring serum creatinine and using a urine dipstick to check protein and glucose concentration before initiating TDF. It is unclear how often creatinine and renal tubular function (urine protein and glucose) should be monitored in asymptomatic patients. Many Panel members monitor creatinine with other blood tests every 3 to 4 months and perform urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and in the absence of proteinuria. Because nephrotoxicity increases with the duration of TDF treatment, monitoring should be continued during long-term therapy with the drug.

Because renal glomerular damage primarily increases the concentration of albumin in urine and proximal renal tubular damage increases the concentration of low-molecular-weight proteins like beta-2 microglobulin in urine, dipstick urinalysis (which primarily measures urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measuring urine albumin and urine protein and calculating the ratio of urine albumin to urine protein can be helpful in identifying the non-albumin proteinuria that is seen in TDF-associated nephrotoxicity.[52,53] Although these more complex and expensive tests may be used in research settings, in clinical practice, using a renal dipstick to identify normoglycemic glycosuria and proteinuria is the easiest way to detect renal damage.

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Zidovudine (ZDV, Retrovir)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Syrup: 10 mg/mL

Capsule: 100 mg

Concentrate for Injection or Intravenous Infusion: 10 mg/mL (Retrovir)

Generic Formulations

- 100-mg capsule
- 10-mg/mL syrup
- 300-mg tablet

Fixed-Dose Combination (FDC) Tablets

- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Note: Zidovudine (ZDV) is frequently used in neonates to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection and Table 12 for information about using ZDV to prevent perinatal transmission.

Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth[a]

Gestational Age at Birth	Oral ZDV Dose
≥35 weeks	**Birth to Age 4 Weeks** • ZDV 4 mg/kg twice daily; *or* • Alternative simplified weight-band dosing **Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth** **Note:** The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.

Selected Adverse Events

- Bone marrow suppression leading to anemia and neutropenia, macrocytosis with or without anemia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of ZDV) and myositis

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develops in patients who are receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- Screen patients for hepatitis B virus (HBV) infection before using FDC products that contain lamivudine

Weight Band	Twice-Daily Volume of ZDV 10 mg/mL Syrup
2 kg to <3 kg	1 mL
3 kg to <4 kg	1.5 mL
4 kg to <5 kg	2 mL

Aged >4 Weeks

- ZDV 12 mg/kg twice daily

≥30 weeks to <35 weeks	**Birth to Age 2 Weeks** • ZDV 2 mg/kg twice daily **Aged 2 Weeks to 6 to 8 Weeks** • ZDV 3 mg/kg twice daily **Aged >6 Weeks to 8 Weeks** • ZDV 12 mg/kg twice daily
<30 weeks	**Birth to Age 4 Weeks** • ZDV 2 mg/kg twice daily **Aged 4 Weeks to 8 to 10 Weeks** • ZDV 3 mg/kg twice daily **Aged >8 Weeks to 10 Weeks** • ZDV 12 mg/kg twice daily

Note: For infants who are unable to tolerate oral agents, the intravenous dose should be 75% of the oral dose, but the dosing interval should remain the same.

Infant (Aged ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery, Weighing ≥4 kg) and Child Dose

Weight-Based Dosing for Zidovudine

Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

Alternative Body Surface Area Dosing

Oral

- ZDV 180 mg to 240 mg per m^2 of body surface area every 12 hours

(3TC). Severe acute exacerbation of HBV infection can occur when 3TC is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking 3TC.

Metabolism/Elimination

- ZDV is eliminated primarily by hepatic metabolism. The major metabolite is ZDV glucuronide, which is renally excreted.
- ZDV is phosphorylated intracellularly to active ZDV-triphosphate.

Zidovudine Dosing in Patients with Hepatic Impairment

- The dose of ZDV may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients who have impaired hepatic function.

Zidovudine Dosing in Patients with Renal Impairment

- A dose adjustment is required for ZDV in patients with renal insufficiency.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min and patients who are on hemodialysis.

Child and Adolescent (Weighing ≥30 kg) and Adult Dose • ZDV 300 mg twice daily **[Combivir and Generic] Lamivudine/Zidovudine** *Child and Adolescent (Weighing ≥30 kg) and Adult Dose* • One tablet twice daily **[Trizivir and Generic] Abacavir/Lamivudine/Zidovudine** *Child and Adolescent (Weighing ≥30 kg) and Adult Dose* • One tablet twice daily	

[a] For premature infants who receive an HIV diagnosis, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Bone marrow suppressive/cytotoxic agents, including ganciclovir, valganciclovir, interferon alfa, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine (ZDV).
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues—such as ribavirin—antagonize *in vitro* antiviral activity of ZDV.
- *Doxorubicin:* Simultaneous use of doxorubicin and ZDV **should be avoided.** Doxorubicin may inhibit the phosphorylation of ZDV to its active form.

Major Toxicities

- *More common:* Hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants who are receiving both lamivudine (3TC) and ZDV than in infants who are receiving only ZDV.[1]
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* Possible increased risk of cardiomyopathy.[2-4]

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ZDV is frequently included as a component of the nucleoside reverse transcriptase inhibitor (NRTI) backbone for antiretroviral therapy (ART), and it has been studied in children in combination with other NRTIs, including abacavir (ABC) and 3TC.[5-8] Pediatric experience with ZDV both for treating HIV and for preventing perinatal transmission is extensive. However, the mitochondrial toxicity of ZDV leads many experts to favor the use of ABC or tenofovir alafenamide in cases where the patient's age and the results of viral resistance testing do not restrict the use of these drugs.

Efficacy in Clinical Trials

The combination of ZDV and 3TC has been extensively studied in children and has been a part of antiretroviral (ARV) regimens in many trials. The safety and efficacy of ZDV plus 3TC were compared to the safety and efficacy of ABC plus 3TC and stavudine (d4T) plus 3TC in children aged <5 years in the CHAPAS-3 (Children with HIV in Africa Pharmacokinetics and Adherence of Simple antiretroviral regimens) study. All regimens also included either nevirapine or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.[9] A number of studies have evaluated the efficacy and toxicity of different dual-nucleoside reverse transcriptase inhibitor backbones used as part of combination ART.[10-12]

Infants with Perinatal HIV Exposure

The Pediatric AIDS Clinical Trials Group (PACTG) 076 clinical trial[13] demonstrated that administering ZDV to pregnant women and their infants could reduce the risk of perinatal HIV transmission by nearly 70%. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection for further discussion on using ZDV to prevent perinatal transmission of HIV. A dose of approximately ZDV 4 mg/kg of body weight every 12 hours is recommended for prevention of perinatal HIV transmission in neonates and infants with gestational ages ≥35 weeks. Infants who have been exposed to HIV but who are uninfected should continue on the prophylactic dose for 4 weeks to 6 weeks, depending on their gestational age at time of delivery and the risk assessment for perinatal transmission.

Simplified, alternative weight-band dosing has also been developed, and the rationale for these doses is based on the intracellular metabolism of ZDV (see Pharmacokinetics below). The rate-limiting step in the phosphorylation of ZDV to active ZDV triphosphate is the limited amount of thymidylate kinase. Increasing the dose of ZDV will lead to increased ZDV plasma concentrations and increased intracellular concentrations of ZDV monophosphate, but not ZDV diphosphate or ZDV triphosphate.

In 31 infants who received ZDV to prevent perinatal transmission, levels of intracellular ZDV metabolites were measured after delivery. Plasma ZDV and intracellular ZDV monophosphate decreased by roughly 50% between post-delivery Day 1 and Day 28, whereas ZDV diphosphate and ZDV triphosphate remained low throughout the sampling period.[14] ZDV dose is poorly correlated with the active form of ZDV that is found intracellularly. Because of this, a simplified weight-band dosing approach can be used for the first 4 weeks of life in infants with gestational ages ≥35 weeks (see the dosing table above). This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during ZDC use in the first 4 weeks of life and will make it easier for caregivers to administer ZDV oral syrup to their infants. The changes in weight and the small differences in ZDV dose will have minor effects on the intracellular concentrations of ZDV triphosphate.

Infants with HIV Infection

The Early Infant Treatment Study in Botswana evaluated the safety and efficacy of initiation of antiretroviral therapy in the first week of life. Forty infants who tested positive for HIV within 96 hours of birth were started on ZDV, 3TC, and nevirapine (NVP) with successful transition to lopinavir/ritonavir (LPV/r) at 2 to 5 weeks after delivery. Early treatment was found to be safe and effective, with most infants achieving and maintaining viral suppression by 24 weeks of age.[15]

For full-term neonates who receive an HIV diagnosis during the first days to weeks of life, the ZDV dose should be increased to the continuation dose at age 4 weeks (see the dosing table above). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically during the first 4 to 6 weeks of life in full-term neonates. This increase in metabolizing enzyme activity leads to an increased clearance of plasma ZDV, and the dose of ZDV should be adjusted when ZDV is used to treat HIV after the first 4 weeks in full-term infants.

For premature infants who receive an HIV diagnosis, the time to increase the ZDV dose from the initial dose varies with post-gestational age and the clinical status of the neonate. On the basis of population pharmacokinetic (PK) modeling and simulations and data from studies that have evaluated ZDV PKs in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends the following:

- For infants with HIV born at ≥30 weeks to <35 weeks, switch to a dose of ZDV 12 mg/kg twice daily at a post-gestational age of 6 weeks to 8 weeks.
- For infants born at <30 weeks, switch to ZDV 12 mg/kg twice daily at a post-gestational age of 8 weeks to 10 weeks.[16]

Clinicians should perform a careful clinical assessment of the infant, evaluate hepatic and renal function, and review concomitant medications before increasing the ZDV dose to the dose recommended for full-term infants.

Pharmacokinetics

ZDV undergoes intracellular metabolism to achieve its active form, ZDV triphosphate. Phosphorylation requires multiple steps: ZDV is phosphorylated by thymidine kinase to ZDV monophosphate, ZDV monophosphate is phosphorylated by thymidylate kinase to ZDV diphosphate, and ZDV diphosphate is phosphorylated by nucleoside diphosphate kinase to ZDV triphosphate. Overall, ZDV PKs in pediatric patients aged >3 months are like those seen in adults. Although the mean half-life of intracellular ZDV triphosphate (9.1 hours) is considerably longer than that of unmetabolized ZDV in plasma (1.5 hours), once-daily ZDV dosing is not recommended because of the low intracellular ZDV triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.[17] PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of ZDV compared with the clearance observed in term newborns of similar postnatal ages.[6] ZDV has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio is 0.68), and ZDV has been used in children with HIV-related CNS disease.[8]

PK and safety of ZDV, 3TC, and LPV/r in children living with HIV and severe acute malnutrition (SAM) was studied in International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1092.[18] Steady-state PK, safety, and tolerability was compared in children with HIV with and without SAM. Overall safety and tolerability did not differ between the two cohorts and similar area- under-the-curve values for ZDV, 3TC, and LPV/r were observed in these children who were dosed according to World Health Organization weight-band dosing recommendations.[18]

Toxicity

Several studies suggest that the adverse hematologic effects of ZDV may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean plasma area-under-the-curve values for ZDV.[5,6,19] A significant reduction in the incidence of hematologic toxicity was observed during a retrospective analysis of infants who received a short course of ZDV (2 weeks) to prevent perinatal HIV transmission.[20] In this study, 137 infants received ZDV for 2 weeks, and 184 infants received ZDV for >2 weeks; of these infants, 168 (91.3%) received 4 weeks of ZDV prophylaxis. The risk of anemia (defined as a Division of AIDS [DAIDS] severity grade of mild or higher) was significantly lower in the short-course group at both age 1 month ($P < 0.001$) and age 3 months ($P < 0.001$).[20] Some national guidelines, including those from Germany/Austria and Great Britain, recommend a minimum of 2 weeks of post-exposure prophylaxis in infants at low risk or very low risk of HIV transmission.[21] Current U.S. guidelines recommend 4 weeks of prophylaxis for infants at low risk of HIV transmission. For infants who develop significant anemia while receiving ZDV for prevention of perinatal HIV transmission, early discontinuation may be considered for infants who are determined to be at a low risk of transmission after expert consultation. A recent study conducted in Thailand evaluated the safety of triple antiretroviral neonatal presumptive therapy with ZDV/3TC/nevirapine for 6 weeks in infants at high risk of acquisition of HIV compared with 4 weeks of monotherapy with ZDV in infants considered at low risk. No significant differences were observed in the incidence of neutropenia, hepatoxicity, or severe anemia between the triple antiretroviral and the ZDV monotherapy groups.[22]

Incidence of hematological toxicity was investigated in the ARROW study, which randomized ART-naive Ugandan and Zimbabwean children to receive either ZDV-containing regimens or ABC-containing regimens. The incidence of severe anemia was similar regardless of ZDV use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. ZDV use was associated with severe neutropenia in a small number of children.[23] In a retrospective study conducted in Ethiopia, an evaluation of predictors of anemia among children on ART[24] was conducted for the time period of 2007 to 2017. Study participants receiving ZDV-containing regimens were four times more likely to develop anemia than those children receiving ABC-containing regimens. Other predictors of anemia in addition to ZDV in this patient population included tuberculosis, severe immunosuppression, and undernutrition.

ZDV is associated with greater mitochondrial toxicity than ABC and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than d4T.[25,26]

Although the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since the use of ART became routine, the use of a regimen that contains ZDV may increase the risk.[2,4] Analysis of data from a U.S.-based, multicenter, prospective cohort study (PACTG 219/219C) found that ongoing ZDV exposure was independently associated with a higher rate of cardiomyopathy.[2] As part of the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, echocardiogram measurements were collected between 2008 and 2010 in 325 youth aged 7 to 16 years with perinatally acquired HIV infection. An association between ZDV use and increased end-systolic wall stress was observed in this study. The investigators speculate that alterations in cardiac structure in these children could progress to symptomatic cardiomyopathy later in life.[3] A large cohort study to evaluate the prevalence of cardiac dysfunction in children and young adults <26 years of age was conducted in Kenya.[4] Approximately 28% of participants were found to have evidence of early cardiac dysfunction. Left ventricular ejection fraction negatively correlated with prior ZDV exposure, detectable HIV RNA, and elevated interleukin-6 concentrations.[4]

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Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Doravirine (DOR, Pifeltro)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant)

Doravirine (DOR, Pifeltro)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Tablet: 100 mg **Fixed-Dose Combination (FDC) Tablet** • [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Child and Adolescent (Weighing ≥35 kg) and Adult Dose • DOR 100 mg once daily in antiretroviral (ARV)-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR **[Delstrigo] Doravirine (DOR)/Lamivudine (3TC)/Tenofovir Disoproxil Fumarate (TDF)** *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* • One tablet once daily in ARV-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to the individual components of Delstrigo	• Nausea • Abdominal pain • Diarrhea • Abnormal dreams • Insomnia, somnolence **Special Instructions** • DOR can be taken with or without food. • **Do not use** DOR with other non-nucleoside reverse transcriptase inhibitors. • When DOR is coadministered with rifabutin, the dose should be increased from DOR 100 mg once daily to DOR 100 mg twice daily. When DOR/3TC/TDF (Delstrigo) is coadministered with rifabutin, an additional 100-mg dose of freestanding DOR needs to be administered approximately 12 hours later. • Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains 3TC and TDF. Severe acute exacerbation of HBV can occur when 3TC or TDF are discontinued; therefore, hepatic function and HBV viral load should be monitored for several months after halting therapy with 3TC or TDF. **Metabolism/Elimination** • DOR is metabolized by the enzyme cytochrome P450 3A.

	• DOR has multiple interactions with several drugs (see Drug Interactions section below). **Doravirine Dosing in Patients with Hepatic Impairment** • Dose adjustment is not required in patients with mild or moderate hepatic impairment. DOR has not been studied in patients with severe hepatic impairment. **Doravirine Dosing in Patients with Renal Impairment** • Dose adjustment is not required when using DOR in patients with mild, moderate, or severe renal impairment. DOR use has not been studied in patients with end-stage renal disease or in patients on dialysis. • DOR administered with 3TC and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Doravirine (DOR) is a cytochrome P450 (CYP) 3A substrate that is associated with several important drug interactions with drugs that are strong CYP3A enzyme inducers. Coadministration with these drugs may cause significant decreases in DOR plasma concentrations and potential decreases in efficacy, which can lead to the development of resistance. Before DOR is administered, a patient's medication profile should be reviewed carefully for potential drug interactions with DOR.[1,2]
- DOR **should not be coadministered** with the CYP3A-inducing non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV), etravirine, and nevirapine.[3,4] In a Phase 1 trial (described below under Efficacy in Clinical Trials), DOR plasma exposure transiently decreased by 62% when DOR was started immediately after stopping EFV. A *post hoc* analysis of the Phase 3 DRIVE-SHIFT study (described below under Efficacy in Clinical Trials), however, showed that at Week 4, DOR plasma levels in patients who had switched from an EFV-based regimen to a DOR-based regimen were similar to DOR plasma levels in patients who switched from a protease inhibitor (PI)–based regimen to a DOR-based regimen (all of the regimens in the study used a backbone of lamivudine [3TC] plus tenofovir disoproxil fumarate [TDF]).[5] A similar effect of prior EFV-based ART on the pharmacokinetics (PK) of DOR was demonstrated in IMPAACT 2014 (described below under Efficacy in Clinical Trials) among adolescents weighing ≥45 kg who switched from EFV-based ART to DOR-based ART with 3TC/TDF.[6,7]
- DOR **should not be coadministered** with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; or St. John's wort.[3,4]
- Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours after a fixed-dose combination of DOR/3TC/TDF or an increase of the DOR dose to 100 mg twice daily.[2-4]

Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams
- *Less common (more severe):* Neuropsychiatric adverse events (AEs), including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

Resistance

The International Antiviral Society-USA maintains a list of updated drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

DOR is expected to have activity against HIV with isolated NNRTI resistance that is associated with mutations at positions 103, 181, or 190. Some single mutations and combinations of viral mutations, however, have been shown to significantly decrease susceptibility to DOR. Specifically, clinical HIV isolates containing the Y188L mutation alone or in combinations with K103N or V106I, combinations of V106A with G190A and F227L, or combinations of E138K with Y181C and M230L have shown ≥100-fold reduction in susceptibility to DOR.[3,4] In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of DOR.

Pediatric Use

Approval

DOR is approved by the U.S. Food and Drug Administration for use in children or adolescents weighing ≥35 kg .[3,4] IMPAACT 2014, an ongoing Phase 1/2 study (described below under Efficacy in Clinical Trials), is evaluating the PKs, safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV.(Best, Yee, et al. 2019, Melvin, Best, et al. 2021)

Efficacy in Clinical Trials

The efficacy of DOR was evaluated using data from four randomized adult clinical trials. The first study was a Phase 2b dose-selection, double-blind trial that enrolled treatment-naive adults with HIV.[8] The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD) in treatment-naive adults[9-11] and one open-label, active-controlled, randomized, noninferiority trial that enrolled virologically suppressed adults on antiretroviral therapy (DRIVE-SHIFT).[12]

The dose-selection trial enrolled treatment-naive adults stratified by HIV RNA level at screening (≤100,000 copies/mL or >100,000 copies/mL) and randomized participants to receive one of four different doses (25 mg, 50 mg, 100 mg, or 200 mg) of once-daily DOR or EFV 600 mg with open-label emtricitabine (FTC) 200 mg/TDF 300 mg. After dose selection at Week 24, all participants were switched to DOR 100 mg and, with additional enrollment, 216 participants were randomized to receive once-daily DOR 100 mg (n = 108) or EFV 600 mg (n = 108) for 96 weeks with FTC/TDF. At Week 24, 72.9% of participants on DOR 100 mg and 73.1% of participants on EFV 600 mg had HIV RNA <40 copies/mL.[8]

In DRIVE-FORWARD, adult subjects received either DOR 100 mg (n = 383) or darunavir 800 mg/ritonavir 100 mg (DRV/r) (n = 383) once daily, each in combination with FTC/TDF or abacavir/3TC.[9] In DRIVE-AHEAD, adult subjects received either coformulated DOR/3TC/TDF (n = 364) or EFV/FTC/TDF (n = 364) once daily.[10] An integrated efficacy analysis from both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 48 demonstrated that 84.1% of patients who were treated with the DOR-based regimen achieved HIV RNA <50 copies/mL, compared with 79.9% of patients who were treated with the DRV/r-based regimen and 80.8% of patients who were treated with EFV/FTC/TDF. Results were similar across different baseline viral loads, genders, races, and HIV-1 subtypes.[10] At Week 96 in the DRIVE-FORWARD trial, 277 (95%) of 292 participants who remained on DOR maintained viral suppression (that is, 73% of the overall 383 participants), whereas 248 (91%) of 273 participants who remained on DRV/r maintained viral suppression (that is, 66% of the overall 383 participants).[11]

In the DRIVE-SHIFT study, adult subjects with HIV who were virologically suppressed for ≥6 months on two nucleoside reverse transcriptase inhibitors plus a boosted PI, boosted elvitegravir or on an NNRTI were randomized to switch to a once-daily, single-tablet regimen of DOR 100 mg/3TC 300 mg/TDF 300 mg or to continue their current therapy (baseline regimen). At Week 24, 93.7% on DOR/3TC/TDF versus 94.6% on baseline regimen had HIV-1 RNA <50 copies/mL (difference −0.9 [−4.7 to 3.0]). At Week 48, 90.8% on DOR/3TC/TDF had HIV-1 RNA <50 copies/mL, demonstrating noninferiority versus baseline regimen at Week 24 (difference −3.8 [−7.9 to 0.3]).[12] Participants were switched on Day 1 (immediate-switch group [ISG]; n = 447) or at Week 24 (delayed-switch group [DSG]; n = 209). Long-term efficacy in the extension arm at Week 144 showed virologic suppression (HIV RNA<50 copies/mL) in 80.1% of ISG (351 out of 438) and 83.7% of DSG (175 out of 209) in FDA snapshot (intent-to-treat) analysis.[13]

IMPAACT 2014 study data in ARV-naive or ARV-experienced virologically suppressed adolescents suggest favorable antiviral effect comparable to adult data.(Melvin, Best et al. 2021) A total of 45 participants, 43 virologically suppressed (50% on EFV-based ART) and 2 ARV-naive adolescents with mean age 15 years (12–17 years), were treated with DOR/3TC/TDF. At Week 24, 42 out of 45 (93.3%; 95% confidence interval [CI], 81.7–98.6) achieved or maintained HIV-1 RNA <40 copies/mL in FDA snapshot (intent-to-treat) analysis, while 42 out of 43 (97.7%; 95% CI, 87.7–99.9) achieved or maintained HIV-1 RNA <40 copies/mL in observed failure (on-treatment) analysis.[7]

Pharmacokinetics

The PKs of DOR have been evaluated in treatment-naive adults aged ≥18 years and both treatment-naive and treatment-experienced adolescents. A Phase 2 trial evaluated DOR across a dose range of 0.25 times to 2 times the recommended dose in treatment-naive participants with HIV who also received FTC/TDF. No exposure-response relationship for efficacy was reported for DOR.[10]

Toxicity

In trials that compared DOR-based regimens and EFV-based regimens, central nervous system (CNS) AEs (dizziness, sleep disorder and disturbances, and altered sensorium) occurred less frequently among the patients who received DOR than among those who received EFV. In the dose-finding trial, CNS AEs were reported in 26.9% of patients on DOR-based regimens, compared with 47.2% of patients on EFV-based regimens at Week 24.[8] In the integrated safety analysis from the DRIVE-FORWARD and DRIVE-AHEAD trials, 25.5% of patients on DOR-based regimens experienced CNS AEs at Week 48, compared with 55.9% of patients on EFV-based regimes.[10,14] Neither DRIVE-FORWARD nor DRIVE-AHEAD included an integrase strand transfer inhibitor–based regimen as an active control. Fewer participants who received DOR-based regimens experienced diarrhea than those treated with DRV/r-based regimens (12.4% vs. 22.5%, respectively). In the DRIVE-SHIFT study, among adults who were receiving a ritonavir-boosted PI at study entry, mean reductions in fasting low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol at Week 24 were significantly greater in people who received DOR/3TC/TDF compared with the baseline PI-based regimen with 3TC/TDF ($P < 0.0001$).[12] The reduction in fasting lipids was maintained through Week 144 in the extension arm of the DRIVE-SHIFT study.[13] Similarly, the 96 weeks of data from the DRIVE-FORWARD trial supported greater mean reductions in low-density lipoprotein cholesterol (−14.6 mg/dL [95% CI, −18.2 to −11.0]) and non-high-density lipoprotein cholesterol (18. 4 mg/dL [95% CI, −22.5 to −14.3]) among participants in the DOR arm than among those in the DRV/r arm.[11]

In the IMPAACT 2014 study of 43 treatment-experienced and 2 ARV-naive adolescents aged 12 to <18 years on DOR/3TC/TDF at Week 24, there were no grade 4 AEs, serious AEs, or premature study discontinuation due to AEs. The single drug-related Grade 1 AE was dizziness, and nine participants had the following drug-unrelated Grade 3 AEs: increased alanine aminotransferase (n = 1); increased creatinine with decreased estimated glomerular filtration rate (eGFR) (n = 2); decreased eGFR (n = 1); gastroenteritis (n = 1); diarrhea (n = 1); and increased blood pressure (n = 4).[7]

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Efavirenz (EFV, Sustiva)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Capsules: 50 mg, 200 mg **Tablet:** 600 mg **Generic Formulations** • 50-mg and 200-mg capsules • 600-mg tablet **Fixed-Dose Combination (FDC) Tablets** • [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg • [Symfi and generic] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg • [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Neonatal Dose • Efavirenz (EFV) is not approved for use in neonates. **Pediatric Dose** • EFV capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules. *Infants and Children Aged 3 Months to <3 Years and Weighing ≥3.5 kg* • The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of EFV in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group. • If the use of EFV is unavoidable due to a clinical situation, the Panel suggests using investigational doses of EFV in this age group (see Table A in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below).	• Rash, which is generally mild and transient • Central nervous system (CNS) symptoms, such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation, late-onset ataxia, and encephalopathy • Gynecomastia • Hepatotoxicity • Corrected QT prolongation • Use of EFV may produce false-positive results with some cannabinoid and benzodiazepine tests. **Special Instructions** • EFV capsules and tablets can be swallowed whole, or EFV capsules can be administered by sprinkling the contents of an opened capsule on food as described below. • Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.

Children Aged ≥3 Years and Weighing ≥10 kg

Once-Daily Doses of Efavirenz by Weight

Weight	EFV Dose[a,b]
10 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg
20 kg to <25 kg	300 mg
25 kg to <32.5 kg	350 mg
32.5 kg to <40 kg	400 mg
≥40 kg	600 mg

[a] The dose in mg can be dispensed in any combination of capsule strengths. Capsules may be administered by sprinkling the contents onto an age-appropriate food (see Special Instructions below).

[b] Some experts recommend a dose of EFV 367 mg per m^2 of body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see the Pediatric Use section below for details). Weight bands approximate a dose of EFV 367 mg per m^2 of body surface area, with a maximum dose of 600 mg.

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- EFV 600 mg once daily

[Atripla] Efavirenz 600 mg/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

[Symfi] Efavirenz 600 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥40 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily
- Take on an empty stomach.

Note: Symfi Lo has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in EFV plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh ≥40 kg. The use of therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric

- Administer EFV, Atripla, Symfi, or Symfi Lo on an empty stomach. Avoid administration with a high-fat meal because this has the potential to increase absorption.
- The U.S. Food and Drug Administration cautions that EFV should not be used during the first trimester of pregnancy because of potential teratogenicity. However, after a review of updated evidence regarding teratogenicity risks, the Perinatal Guidelines do not restrict use of EFV in female adolescents and adults who are pregnant or who may become pregnant.

Instructions for Using the Efavirenz Capsule as a Sprinkle Preparation with Food or Formula

- Hold capsule horizontally over a small container and carefully twist open to avoid spillage.
- Gently mix capsule contents with 1 to 2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

Metabolism/Elimination

- Cytochrome P450 (CYP) 2B6 is the primary enzyme for EFV metabolism.
- CYP3A and CYP2B6 inducer *in vivo*
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP, particularly CYP2B6 polymorphisms. Slower metabolizers are at higher risk of toxicity. See the Therapeutic Drug Monitoring section below for information about the management of mild or moderate toxicity.

Efavirenz Dosing in Patients with Hepatic Impairment

- EFV **is not recommended** for patients with moderate or severe hepatic impairment.

Atripla, Symfi, and Symfi Lo Dosing in Patients with Renal Impairment

- Because Atripla, Symfi, and Symfi Lo are FDC products containing TDF, lamivudine, and/or emtricitabine that require dose adjustments based on renal function, they should not be used in patients with creatinine clearance <50 mL/min or in patients on dialysis.

patients who weigh ≥40 kg (see the Therapeutic Drug Monitoring section below).	

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism*: Coadministration of efavirenz (EFV) with drugs that are primarily metabolized by cytochrome P450 (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the coadministered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of EFV, resulting in lower plasma concentrations. There is potential for multiple drug interactions with EFV. Importantly, dose adjustment or the addition of ritonavir may be necessary when EFV is used in combination with atazanavir (ATV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).
- Before EFV is administered, a patient's medication profile should be reviewed carefully for potential drug interactions with EFV.
- Corrected QT (QTc) prolongation has been observed with the use of EFV.[1,2] An alternative to EFV should be considered in patients who are receiving a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

Major Toxicities

- *More common:* Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities—such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, and seizures—have been reported, primarily in adults. See Table 15a. Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity for information on managing these toxicities.
- *Rare:* QTc prolongation has been observed with the use of EFV, and Torsades de Pointes has been reported with EFV use.[3] An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

EFV has been approved by the U.S. Food and Drug Administration (FDA) for use as part of antiretroviral (ARV) therapy in children aged ≥3 months and weighing ≥3.5 kg. The FDA has also approved the use of Symfi Lo, the fixed-dose combination of EFV 400 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing ≥35 kg.

Efficacy in Clinical Trials

EFV-based regimens have proven virologically superior or noninferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, ATV, elvitegravir, raltegravir, and MVC.[4-10] EFV was shown to be inferior to dolutegravir (DTG) in the SINGLE trial in adults, which compared the virologic response of DTG plus abacavir/3TC with the virologic response of EFV/TDF/emtricitabine (FTC) at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the EFV group.[11]

In clinical trials in adults and children with HIV, EFV used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. FDA approval of Symfi (EFV 600 mg/3TC/TDF) was based on the results from a clinical trial that compared the use of TDF with the use of stavudine when each drug was administered with 3TC and EFV.[12] This trial showed that these regimens were similarly effective. The 96-week results of the Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy (ENCORE) 1 trial, a randomized trial in adults, showed that EFV 400 mg used in combination with TDF and FTC was noninferior to EFV 600 mg used in combination with TDF and FTC.[13] EFV used in combination either with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety comparable to what has been seen in adults.[14-16]

FDA approval of Symfi Lo was based on a comparison between EFV 400 mg and EFV 600 mg, both taken with FTC 200 mg plus TDF 300 mg in 630 ARV-naive adult participants with a mean age of 36 years (range 18–69 years). Sixty-eight percent of participants were male, 37% were of African heritage, 33% were of Asian ethnicity, 17% were Hispanic, and 13% were White. This study showed similar rates of viral load suppression and toxicities among participants in each group.[13] Because EFV clearance is related to age and CYP2B6 polymorphisms, and because allele frequency varies by ethnicity, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) suggest using therapeutic drug monitoring (TDM) when using Symfi Lo in pediatric patients weighing ≥40 kg.

Pharmacokinetics: Pharmacogenomics

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of EFV may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for EFV metabolism, and pediatric patients with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher EFV levels in these patients than in those with the G/G or G/T genotypes.[17-20] The CYP2B6-516-T/T allele frequency varies by ethnicity. In a study of adults from the United States and Italy, this allele had a frequency of 24.4% among White study participants, a frequency of 31.3% among Black study participants, and a frequency of 34.9% among Hispanic study participants.[21] A retrospective study of pediatric patients in a multiethnic, high-income setting confirmed that EFV plasma concentrations can vary among patients. The interindividual variability could be explained in large part by polymorphisms in drug metabolizing genes, as well as by age at treatment initiation and time since treatment initiation.[22] International Material Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1070 has shown that aggressive dosing with approximately 40 mg/kg of EFV using opened capsules resulted in therapeutic EFV concentrations in 58% of children aged <3 years with the G/G or G/T genotypes, but excessive exposure occurred in those with the T/T genotype.[23] Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see *Pharmacokinetics and Dosing: Infants and Children Aged <3years* discussion below).[20,23]

Other variants, CYP2B6 alleles and variant CYP2A6 alleles, have been found to influence EFV concentrations in adults and children.[20,24-27]

Pharmacokinetics and Dosing: Infants and Children Aged <3 Years

The Panel **does not recommend** the use of EFV in children aged 3 months to <3 years. Limited pharmacokinetic (PK) data in children aged <3 years or weighing <13 kg have shown that it is difficult to achieve target trough concentrations in this age group.[18,28] These data show age-related differences in absorption and the impact of formulation on EFV PKs.[19] Also, hepatic enzyme activity is known to change with age. Using a pharmacometric model, the increase in oral clearance of EFV as a function of age is predicted to reach 90% of mature value by age 9 months.[19] This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.[19] The CYP2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP2B6 when compared with the CYP2B6-516-G/T or -T/T genotype.[17] In children with the CYP2B6-516-G/G genotype, the oral clearance rate of EFV has been shown to be higher in children aged <5 years than in older children.[17] Efficacy data for opened capsules with contents used as a sprinkle preparation suggest acceptable palatability and bioavailability for infants and children aged <3 years; however, the difficulty associated with sprinkling the contents of opened capsules contributes to the variability of PK measures in this age group.

IMPAACT P1070 studied children aged <3 years with HIV and tuberculosis (TB) coinfection using doses of EFV that were determined by weight band based on CYP2B6-516-G/G and -G/T genotypes: children with G/G and G/T genotypes were considered extensive metabolizers (EMs), and children with T/T genotypes were considered slow metabolizers (SMs) (see Table A below). When doses were used without regard to genotype, a dose of approximately 40 mg/kg per day resulted in therapeutic EFV concentrations in an increased proportion of study participants with G/G or G/T genotypes but excessive exposure in a high proportion of participants with T/T genotypes. This dose is higher than the FDA-approved dose of EFV.[23] Therefore, doses were modified so that infants and young children with the T/T genotype received a reduced dose. The doses listed for P1070 in Table A are investigational.

A recent study evaluated the PKs of EFV in children aged <3 years who had TB/HIV coinfection and were receiving anti-TB treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol. The findings from this study reinforced the use of CYP2B6-516 genotype-directed EFV dosing and showed that, in general, the EFV weight-band dose did not need to be modified further for children aged <24 months. Dosing for children aged 24 to 36 months requires further investigation.[29]

Investigational Dosing for Children Aged 3 Months to <3 Years by CYP2B6 Genotype

Table A. Comparison of Efavirenz Doses Used in P1070 and the FDA-Recommended Doses

Weight	Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (EMs)[a]	Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (SMs)[a]	FDA-Approved Dosing for Children Aged 3 Months to <3 Years (Without Regard to CYP2B6 Genotype)
5 kg to <7 kg	300 mg	50 mg	150 mg
7 kg to <7.5 kg	400 mg	100 mg	150 mg
7.5 kg to <10 kg	400 mg	100 mg	200 mg
10 kg to <14 kg	400 mg	100 mg	200 mg
14 kg to <15 kg	500 mg	150 mg	200 mg
15 kg to ≤17 kg	500 mg	150 mg	250 mg

[a] Investigational doses are based on the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) study P1070.[23,29] Evaluation of CYP2B6 genotype is required before initiating efavirenz (EFV). Therapeutic drug level monitoring is recommended, with a trough concentration measured 2 weeks after initiating EFV and again at age 3 years for a possible dose adjustment.

Key: CYP = cytochrome P450; EM = extensive metabolizer; SM = slow metabolizer

The FDA-approved doses of EFV for use in infants and children aged 3 months to <3 years were derived from a population PK model that was based on data from older subjects in the Pediatric AIDS Clinical Trials Group (PACTG) 1021 and PACTG 382, as well as from data collected during AI266-922, a study that assessed the PKs, safety, and efficacy of using capsule sprinkles in children aged 3 months to 6 years (see Table A). The FDA-approved doses are lower than the CYP2B6 EM doses and higher than the CYP2B6 SM doses from the P1070 study. PK modeling, based on P1070 PK data, was used to generate estimates of the percentage of participants who were likely to reach therapeutic EFV target concentrations on FDA-indicated doses, according to the participants' genotypes.[23] The study reported that an estimated one-third of EM children who received the FDA-approved dose would experience subtherapeutic EFV exposures, and more than half of SM children who received the FDA-approved dose would have area under the curve (AUC) values that were above the target range.

The Panel **does not recommend** use of EFV in children aged 3 months to <3 years. If the clinical situation demands the use of EFV, the Panel recommends determining CYP2B6 genotype prior to use (see a list of laboratories that perform this test). Patients should be classified as extensive CYP2B6-516-G/G and -G/T genotype metabolizers or slow CYP2B6-516-T/T genotype metabolizers to guide dosing, as indicated by the investigational doses from IMPAACT study P1070 (see Table A). Whether the doses used are investigational or approved by the FDA, EFV plasma concentrations should be measured 2 weeks after initiating EFV (see the Therapeutic Drug Monitoring section below). The mid-dose EFV plasma concentration target of 1.0 mg/L to 4.0 mg/L derived from adult clinical monitoring data also, typically, is applied to trough concentrations. A study of 128 African children (aged 1.7–13.5 years) suggests that the concentration at 24 hours (C_{24h}) threshold for increased risk of unsuppressed viral load[30] is C_{24h} 0.65 mg/L. Consultation with an expert in pediatric HIV infection is recommended before adjusting the dose. In addition, when following the P1070 investigational dose recommendations, some experts would measure EFV concentrations at age 3 years before transitioning the child to the recommended dose for children aged ≥3 years.

Pharmacokinetics: Children Aged ≥3 Years and Adolescents

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, EFV concentrations can be suboptimal.[17,31-35] Therefore, some experts recommend using TDM in patients who are receiving EFV and possibly using higher doses in young children, especially in certain clinical situations, such as virologic rebound or lack of response in an adherent patient. In one study in which the EFV dose was adjusted in response to measurement of the AUC, the median administered dose was EFV 13 mg/kg (367 mg per m^2 of body surface area), and the range was from 3 mg/kg to 23 mg/kg (69–559 mg per m^2 of body surface area).[36]

Toxicity: Children Versus Adults

The toxicity profile for EFV differs for adults and children. One adverse effect (AE) commonly seen in children is rash, which was reported in up to 40% of children and 27% of adults.[37] The rash is usually maculopapular, pruritic, mild to moderate in severity, and rarely requires drug discontinuation. Onset is typically during the first 2 weeks of treatment. Although severe rash and Stevens-Johnson syndrome have been reported, they are rare.

Multiple studies in adults have shown that EFV use is associated with low vitamin D levels, and several studies have found an association between EFV use and low bone mineral density.[38-41] Efavirenz induces CYP3A4 and CYP24 enzymes that may affect vitamin D homeostasis. Because of these findings, the Panel recommends measurement of vitamin D in patients receiving EFV and vitamin D supplementation for those with vitamin D deficiency (see Table 15j.Osteopenia and Osteoporosis).

In adults, CNS symptoms are commonly reported and affected 29.6% of patients in one meta-analysis of randomized trials.[42] These symptoms usually occur early in treatment and rarely require drug discontinuation, but they sometimes can persist for months. Administering EFV at bedtime appears to decrease the occurrence and severity of these neuropsychiatric AEs. For patients who can swallow capsules or tablets, ensuring that EFV is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. In several studies, the incidence of neuropsychiatric AEs was correlated with EFV plasma concentrations, and the symptoms occurred more frequently in patients with higher concentrations.[43-46] The ENCORE1 study in adults demonstrated that a dose of EFV 400 mg is associated with fewer AEs and a noninferior virologic response when compared with the recommended 600-mg dose of EFV.[13,47] A Tanzanian study of children aged 6 to 12 years showed that those who were receiving EFV, especially doses of EFV that were higher than or equal to those recommended by the World Health Organization, had more anxiety and more difficulty concentrating at school than children who were receiving alternative ARV medications.[48] Adverse CNS events occurred in 14% of children who received EFV in clinical studies[49] and in 30% of children[50] with plasma EFV concentrations >4 mg/L. Late-onset neurotoxicity, including ataxia and encephalopathy, may occur months to years after initiating EFV. Some events of late-onset neurotoxicity have occurred in patients with certain CYP2B6 genetic polymorphisms who received standard doses of EFV. These polymorphisms have been associated with slow metabolism of EFV and increased EFV levels (see the package insert for EFV).

An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the Strategic Timing of AntiRetroviral Treatment (START) Trial, a prospective analysis of adults.[51,52] This association, however, was not found in the analyses of two large observational cohorts,[53,54] and no cases of suicide were reported in a systematic review of randomized trials.[42] In patients with pre-existing psychiatric conditions, EFV should be used cautiously.

Toxicity: QTc Prolongation

The effect of EFV on the QTc interval was evaluated in a study of 58 healthy adult participants; a variety of CYP2B6 polymorphisms was represented within this group. A positive relationship between EFV concentration and QTc prolongation was observed.[1] Clinicians should consider using an alternative to EFV in patients who are receiving a drug that has a known risk of Torsades de Pointes (e.g., quinidine, clarithromycin) or in patients who are at higher risk for Torsades de Pointes.[2]

Therapeutic Drug Monitoring

It is reasonable for a clinician to use TDM to determine whether a patient is experiencing toxicity, because the concentration of EFV is higher than the normal therapeutic range for some toxicities.[55,56] Dose reduction or drug discontinuation would be considered appropriate management of drug toxicity. Dose reduction is best performed in consultation with an expert in pediatric HIV. Also, TDM should be considered when administering EFV to children aged 3 months to <3 years due to increased oral clearance and variable PK properties in this young age group. TDM should also be considered when using a lower dose of EFV—such as the dose found in Symfi Lo—in children weighing ≥40 kg. Two weeks after initiating EFV in patients aged <3 years, clinicians should measure the plasma concentration of EFV. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting the dose. If a child initiated EFV at an investigational dose at <3 years of age, some experts would also measure plasma concentration at age 3 years, after the child transitions to the recommended dose for children aged ≥3 years.

The currently accepted minimum effective concentration of EFV is a mid-dose concentration (C_{12h}) >1 mg/L in adults, and concentrations of >4.0 mg/L are associated with CNS side effects.[44] However, the validity of using a single target has been called into question.[57] In addition, a lower limit of C_{12h} >0.7mg/L was most predictive of virologic outcome in a study of 180 adults.[58] Findings from a study of 128 African children (aged 1.7–13.5 years) suggest that the C_{24h} threshold for increased risk of unsuppressed viral load is C_{24h} 0.65 mg/L.[30]

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Etravirine (ETR, Intelence)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Tablets: 25 mg, 100 mg, 200 mg

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate and Infant Dose

- Etravirine (ETR) is not approved for use in neonates or infants.

Child Dose

- ETR is not approved for use in children aged <2 years.

Etravirine Dosing Table for Antiretroviral Therapy-Experienced Children and Adolescents Aged 2 to 18 Years and Weighing ≥10 kg

Body Weight	Twice-Daily Dose
10 kg to <20 kg	100 mg
20 kg to <25 kg	125 mg
25 kg to <30 kg	150 mg
≥30 kg	200 mg

- ETR is approved for use in children and adolescents who are treatment experienced. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends that ETR is used as part of a regimen that includes a ritonavir (RTV)-boosted protease inhibitor (PI) (see Efficacy in Clinical Trials and Drug Interactions below).
- Cobicistat-boosted PIs, non-nucleoside reverse transcriptase inhibitors, bictegravir, and elvitegravir/cobicistat should not be used with ETR. Raltegravir and dolutegravir should only be used with ETR with RTV-boosted atazanavir, darunavir, or lopinavir.

Adult Dose for Antiretroviral Therapy-Experienced Patients

- ETR 200 mg twice daily with food

Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional symptoms, and, sometimes, organ dysfunction, including hepatic failure

Special Instructions

- ETR tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.
- Always administer ETR with food. Area under the curve of ETR is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to ETR.
- Swallowing ETR tablets whole is the preferred means of administration. Although the package insert contains instructions for dispersing ETR tablets in water or other liquids, using this administration method generally results in lower ETR exposures compared with swallowing tablets whole. Children who receive dispersed ETR tablets should switch to swallowing tablets whole as soon as developmentally able.

Metabolism/Elimination

- ETR is an inducer of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, CYP2C9, and CYP2C19.
- ETR is involved in multiple interactions with antiretroviral agents and other drugs (see Drug Interactions below).

	Etravirine Dosing in Patients with Hepatic Impairment
	Etravirine Dosing in Patients with Hepatic Impairment • No dose adjustment is required when using ETR in patients with mild or moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment. **Etravirine Dosing in Patients with Renal Impairment** • No dose adjustment is required when using ETR in patients with renal impairment.

Drug Interactions

Additional information about drug interactions is available in Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Etravirine (ETR) is associated with multiple drug interactions. A patient's medication profile should be carefully reviewed for potential drug interactions before ETR is administered.
- ETR **should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, unboosted protease inhibitors (PIs), or cobicistat-boosted PIs.[1]
- ETR **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine [NVP], efavirenz [EFV], rilpivirine, doravirine).
- ETR **should not be administered** with bictegravir or elvitegravir/cobicistat. ETR reduces the trough concentration of raltegravir[2] (RAL) and dolutegravir (DTG). RAL and DTG should be used with ETR only when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.

Major Toxicities

- *More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly during the first 6 weeks of therapy. Rash generally resolves after 1 week to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with ETR. However, patients who have a history of severe rash with prior NNRTI use **should not receive ETR.**
- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme all have been reported. Instances of severe rash have included Stevens-Johnson syndrome, and HSRs have included constitutional symptoms and organ dysfunction, including hepatic failure. Discontinue ETR immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and eosinophilia). Clinicians should monitor a patient's clinical status, including levels of liver transaminases, and initiate appropriate therapy when necessary. Continuing to use ETR after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using NVP or EFV **should not receive ETR.**

Resistance

The International AIDS Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ETR is approved by the U.S. Food and Drug Administration for use in antiretroviral therapy (ART)-experienced children and adolescents aged 2 to 18 years.

Efficacy in Clinical Trials

In the Paediatric study of Intelence As an NNRTI Option (PIANO) study,[3] ART-experienced children aged 6 years to <18 years received ETR with a ritonavir (RTV)-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL, and 52% had HIV RNA <50 copies/mL. At Week 48, 56% of the participants had HIV RNA <50 copies/mL and a mean increase in their CD4 T lymphocyte (CD4) cell counts of 156 cells/mm^3 from baseline. At Week 48, 68% of children aged 6 years to <12 years had plasma HIV RNA <50 copies/mL, whereas only 48% of adolescents aged 12 years to <18 years achieved a plasma viral load of <50 copies/mL.

In a retrospective study of 23 adolescents and young adults in Spain receiving ETR-based therapy, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.[4]

In the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) P1090 trial,[5] ART-experienced children aged ≥2 years to <6 years received ETR with an RTV-boosted PI as part of an optimized background regimen. Participants received ETR at a dose of 100 mg twice daily (10 kg to <20 kg) or 125 mg twice daily (20 kg to <25 kg). At Week 48, 75% had an HIV-1 RNA <400 copies/mL or a >2-log reduction in HIV-1 RNA from baseline. The mean increase in CD4 count and CD4 percentage over 48 weeks was 298.5 cells/mm^3 and 5.2%, respectively. Due to the PIANO and IMPAACT P1090 study findings, if ETR is utilized to treat an ART-experienced child or adolescent, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that ETR is part of a regimen that includes a RTV-boosted PI plus an optimized background regimen.

Pharmacokinetics

In a Phase 1 dose-finding study that involved children aged 6 to 17 years, 17 children were given ETR 4 mg/kg twice daily. The study reported that two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose ($AUC_{0–12h}$) and minimum plasma concentration (C_{min})—were lower than the corresponding parameters observed in adults during previous studies.[6] However, a higher dose (ETR 5.2 mg/kg twice daily; maximum 200 mg per dose) yielded acceptable parameters and was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean $AUC_{0–12h}$) remained lower in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either White or Black participants. In the PIANO study, children and adolescents with ETR concentrations in the lowest quartile (<2,704 ng·h/mL or pre-dose concentration [C_{0h}] <145 ng/mL) were less likely to achieve sustained virologic responses (defined as plasma viral loads

<50 copies/mL) after 48 weeks of treatment than those with ETR concentrations in the upper three quartiles.[7]

Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily with an Optimized Background Regimen, Including a Ritonavir-Boosted Protease Inhibitor[7]

Population	Mean ETR $AUC_{0–12h}$ (ng·h/mL)	Mean ETR C_{0h} (ng/mL)
Children Aged 6–11 Years (n = 41)	5,684	377
Adolescents Aged 12–17 Years (n = 60)	4,895	325
Adults (n = 575)	5,506	393

Key: $AUC_{0–12h}$ = area under the curve for 12 hours post-dose; C_{0h} = pre-dose concentration; ETR = etravirine

IMPAACT P1090 examined the PK and safety of ETR in treatment-experienced children with HIV aged ≥2 years to <6 years.[5] All participants received ETR as part of an optimized background regimen, which included a RTV-boosted PI. The tablets were swallowed whole or dispersed in liquid. ETR was initially given at a dose of 5.2 mg/kg twice daily to a cohort of six children; however, at this dose, the geometric mean ETR $AUC_{0–12h}$ values fell below the target range of 60% of the values seen in adults. Subsequent participants were given twice-daily doses of ETR that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg twice daily, and children weighing 20 kg to <25 kg were given 125 mg twice daily.

The protocol-specified PK targets for ETR were achieved at these doses; the geometric mean $AUC_{0–12h}$ was 3,823 ng·hr/mL, which was within the target range of 2,713 ng·hr/mL to 6,783 ng·hr/mL (60% to 150% of the $AUC_{0–12h}$ value seen in adults). However, considerable intersubject variability was observed, with 5 (33.3%) of 15 participants having $AUC_{0–12h}$ values that were below the 10th percentile for the adult $AUC_{0–12h}$ range (<2,350 ng·hr/mL). The ETR $AUC_{0–12h}$ values were significantly lower in children who received dispersed tablets than in children who swallowed intact tablets: 2,919 ng·hr/mL (n = 11) versus 10,982 ng·hr/mL (n = 3), respectively (P = 0.0008). The Panel recommends that children swallow tablets whole (rather than dispersed in liquid) as soon as developmentally able.

Six children with HIV aged 1 year to <2 years also were enrolled in IMPAACT P1090. Although the ETR exposures satisfied protocol-defined PK targets ($AUC_{0–12h}$ between 2,713 ng·hr/mL and 6,783 ng·hr/mL), they were lower in these children compared with historical data in adults and adolescents (geometric mean ETR $AUC_{0–12h}$ of 3,328 ng·hr/mL). Virologic failure, which was defined as a confirmed viral load of ≥400 copies/mL or less than a 2-log reduction in HIV-1 RNA from baseline, occurred in four of six children by Week 48. Thus, the Panel does not recommend the use of ETR in those younger than 2 years of age.

Given that both the PIANO and IMPAACT P1090 trials were conducted in children receiving RTV-boosted PIs as part of their optimized background regimens, the Panel recommends using ETR as part of a regimen that includes an RTV-boosted PI.

Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions that were deemed to be possibly related to the use of ETR. Rash (Grade 2 or higher) occurred in 13% of pediatric subjects and emerged at a median of 10 days, lasting a median of 7 days. Rash was observed more frequently in female patients (13 of 64 patients; 20.3%) than in male patients (2 of 37 patients; 5.4%).[7] In IMPAACT P1090, adverse drug reactions that were reported for children aged ≥2 years to <6 years were comparable in frequency, type, and severity to those reported for adults. Twelve participants (46.2%) developed Grade 1 or 2 rashes within the first 48 weeks of ETR, but no subject discontinued the study prematurely due to rash. Diarrhea occurred in 8 (30.8%) of 26 patients.[5]

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Nevirapine (NVP, Viramune)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Oral Suspension: 10 mg/mL

Tablets: Immediate-release 200-mg tablets; extended-release (XR) 100-mg and 400-mg tablets

Generic Formulations

- 10 mg/mL suspension
- Immediate-release 200-mg tablets
- XR 400-mg tablets

The oral suspension formulation of nevirapine (brand name Viramune) is not typically stocked in local pharmacies or hospitals. Clinicians should direct pharmacies to ask their drug wholesaler to order it from the Boehringer-Ingleheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

Dosing Recommendations

Note: Nevirapine (NVP) often is used to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection.

Child and Adolescent Dose

- In most situations, NVP is given once daily for 2 weeks to allow autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years.[a]
- See Special Considerations for Dosing: Neonates and Premature Infants below.

Immediate-Release Tablets and Oral Suspension

Gestational Age of 32 to <34 Weeks

- Birth to age 2 weeks: NVP 2 mg/kg per dose twice daily (no lead-in dosing)[a]
- Age 2 to 4 weeks: NVP 4 mg/kg per dose twice daily
- Age 4 to 6 weeks: NVP 6 mg/kg per dose twice daily
- Age >6 weeks: NVP 200 mg/m^2 of body surface area (BSA) per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) based on the review of pharmacokinetic (PK) modeling and simulation data. This dosing strategy has not been evaluated in clinical trials and is not approved by the U.S. Food and Drug Administration (FDA).

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis[b]
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

Special Instructions

- The oral suspension must be shaken well before administering, and it should be stored at room temperature.
- NVP can be given without food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until the rash resolves (see Major Toxicities below).
- Extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Dosing below).
- Most cases of NVP-associated hepatic toxicity occur during the first 12 weeks of therapy;

Gestational Age of 34 to <37 Weeks

- Birth to age 1 week: NVP 4 mg/kg per dose twice daily (no lead-in dosing)[a]
- Age 1 week to 4 weeks: NVP 6 mg/kg per dose twice daily
- Age >4 weeks: NVP 200 mg/m² of BSA per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel based on the review of PK and safety data on this regimen from clinical trials. This dosing strategy is not approved by the FDA.

Gestational Age of ≥37 Weeks to Age of <1 Month

- Birth to age 4 weeks: NVP 6 mg/kg per dose twice daily (no lead-in dosing)[a]
- Age >4 weeks: NVP 200 mg/m² of BSA per dose twice daily; only make this dose increase for infants with confirmed HIV infection.
- This dosing strategy is recommended by the Panel based on the review of PK and safety data on this regimen from clinical trials. This dosing strategy is not approved by the FDA.

Aged ≥1 Month to <8 Years

- NVP 200 mg/m² of BSA per dose twice daily after lead-in dosing.[a] In children aged ≤2 years, some experts initiate NVP without lead-in dosing (maximum dose of immediate-release tablets is NVP 200 mg twice daily).

Aged ≥8 Years

- NVP 120 mg to 150 mg/m² of BSA per dose twice daily after lead-in dosing[a] (maximum dose of immediate-release tablets is NVP 200 mg twice daily).
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose can be left static to achieve the appropriate mg-per-m² dose as the child grows, if no adverse effects emerge.

Extended-Release Tablets

Aged ≥6 Years

- Patients aged ≥6 years who are already taking immediate-release NVP tablets twice daily can be switched to extended-release NVP tablets without lead-in dosing.[a]

Body Surface Area Dosing for Extended-Release Nevirapine Tablets

Body Surface Area	Once-Daily Dose
0.58 m² to 0.83 m²	NVP 200 mg (two 100-mg tablets)
0.84 m² to 1.16 m²	NVP 300 mg (three 100-mg tablets)
≥1.17 m²	NVP 400 mg (one 400-mg tablet)

frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see Major Toxicities below).

Metabolism/Elimination

- NVP is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of an NVP dose is eliminated in urine as uridine diphosphate glucuronosyltransferase (UGT)-derived glucuronidated metabolites.

Nevirapine Dosing in Patients with Hepatic Impairment

- NVP should not be administered to patients with moderate or severe hepatic impairment.

Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis

- An additional dose of NVP should be given following each dialysis session.

Adolescent and Adult Dose • NVP 200 mg twice daily or NVP 400 mg with the extended-release tablets once daily after lead-in dosing.[a,b] **Nevirapine Used in Combination with Lopinavir/Ritonavir** • A higher dose of lopinavir/ritonavir may be needed in patients who also are receiving NVP (see the Lopinavir/Ritonavir section).	

[a] NVP is usually initiated at a lower dose that is increased in a stepwise fashion. NVP induces cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians generally should initiate therapy with the immediate-release tablet formulation once daily instead of twice daily for the first 14 days of therapy. If no rashes or other adverse effects emerge after 14 days of therapy, increase the dose of NVP to the age-appropriate full dose of the immediate-release tablet formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged ≥1 month to <8 years is NVP 200 mg/m² of body surface area (BSA) once daily for the first 14 days, followed by NVP 200 mg/m² of BSA twice daily thereafter. However, in children aged ≤2 years, some experts initiate NVP without lead-in dosing (see the Dosing Considerations: Lead-In Dosing and Special Considerations for Dosing: Neonates and Premature Infants sections below). In patients who are already receiving the full, twice-daily dose of the immediate-release tablets, extended-release tablets can be used without the lead-in period. Patients must swallow extended-release tablets whole. They must not be chewed, crushed, or divided. **Patients must never take more than one form of NVP at the same time.** The dose should not exceed NVP 400 mg daily.

[b] Severe, life-threatening, and, in rare cases, fatal hepatotoxicity—including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure—have occurred in patients who were taking NVP. These toxicities are less common in children than adults. Most cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Nevirapine (NVP) induces hepatic cytochrome P450 (CYP), including 3A and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, leading to a 1.5-fold to twofold increase in NVP clearance. Multiple drug interactions with NVP are possible. Some genetic polymorphisms of CYP2B6 are associated with increased NVP serum concentrations. CYP2B6 polymorphisms vary among populations and may contribute to differences in NVP exposure. See the Efavirenz section for more information on how polymorphisms can alter enzyme activity.
- NVP should not be coadministered to patients who are receiving atazanavir (ATV) (with or without ritonavir), because NVP substantially decreases ATV exposure.
- NVP increases the metabolism of lopinavir (LPV). A dose adjustment of LPV is recommended when the two drugs are coadministered (see the Lopinavir/Ritonavir section).
- Before NVP is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

The following toxicities are seen with continuous dosing regimens, not during single-dose NVP prophylaxis.

- *More common:* Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and elevated hepatic transaminases. In the two largest case series of NVP-induced Stevens-Johnson syndrome in children, the incidence rate was estimated between 1.4% and 7.1%.[1,2] NVP should be **discontinued and not restarted** in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated levels of hepatic transaminases. NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until rash resolves. However, the risk of developing NVP resistance with extended lead-in dosing is unknown, and this concern must be weighed against the current antiviral response and a patient's overall ability to tolerate the regimen.
- *Less common (more severe):* Severe, life-threatening, and, in rare cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. These toxicities are less common in children than adults. Most cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction (HSR). Risk factors for NVP-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C virus infection, female sex, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). Children with CD4 percentages >15% have a threefold increase in the risk of rash and hepatotoxicity after initiating NVP.[3] HSRs have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.
- *Less common (more severe):* In a cross-sectional study of 201 children with HIV aged 6 to 16 years, 43% of whom had hypertension, the use of NVP was associated with left ventricular hypertrophy (LVH) (adjusted odds ratio 3.14; confidence interval, 1.13–8.72; $P = 0.03$) but not left ventricular diastolic dysfunction.[4] The median duration on antiretroviral therapy (ART) in this cohort was 4.7 years (interquartile range 2.6–6.4 years). Most participants (76.6%) were receiving a regimen that included two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, the use of NVP was not associated with LVH in a more recent study by the same authors. LVH has been associated with NVP use in adults.[5,6]

Resistance

The International AIDS Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

NVP is approved by the U.S. Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of ART, especially in resource-limited settings.[7-15] The extended-release tablet formulation has been approved by the FDA for use in children aged ≥6 years.

Efficacy in Clinical Trials

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to NVP in young children but not in older children. IMPAACT P1060 demonstrated the superiority of LPV/r over NVP in children aged <3 years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics showed no differences in virologic outcomes between an NNRTI-based regimen (with either NVP or efavirenz [EFV]) and a protease inhibitor (PI)-based regimen in older children with HIV.[16-22]

In infants and children who were previously exposed to a single dose of NVP to prevent perinatal HIV transmission, NVP-based ART is less likely to control viral load than LPV/r-based ART. In IMPAACT P1060, 153 children with HIV and previous exposure to NVP for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine (ZDV) and lamivudine (3TC) plus either NVP or LPV/r. At 24 weeks post-randomization, 24% of children in the NVP arm had experienced virologic failure compared with 7% of children in the LPV/r arm ($P = 0.0009$); virologic failure was defined as <1 $\log_{10}$ decrease in HIV RNA during Weeks 12 to 24 or HIV RNA >400 copies/mL at Week 24. When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the NVP arm met a primary endpoint compared with 22% of children in the LPV/r arm ($P = 0.027$).[19] Similar results were reported in a randomized trial that compared NVP and LPV/r in children aged 6 to 36 months who had not been previously exposed to NVP. This finding suggests that LPV/r-based therapy is superior to NVP-based therapy for infants, regardless of past NVP exposure.[16]

Extended-release NVP tablets (400 mg) were approved by the FDA for use in children aged ≥6 years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, nonrandomized, crossover trial performed in 85 pediatric participants with HIV. The participants had received at least 18 weeks of immediate-release NVP tablets and had plasma HIV RNA <50 copies/mL prior to enrollment. Participants were stratified according to age (3 years to <6 years, 6 years to <12 years, and 12 years to <18 years). Participants received immediate-release NVP tablets for 11 weeks. Participants were then treated with NVP extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PKs) were determined.[23] Forty participants who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of extended-release NVP tablets through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with extended-release tablets,[24] all 39 participants continued to have plasma HIV RNA <50 copies/mL.

General Dosing Considerations

Body surface area (BSA) has traditionally been used to guide NVP dosing in infants and young children. It is important to avoid underdosing NVP, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both NVP and EFV. Younger children (aged ≤8 years) have higher apparent oral clearance than older children. To achieve drug exposures that are equivalent to those seen in children aged >8 years, younger children require higher doses of NVP than older children.[12,13] Because of this, it is recommended that children aged <8 years receive NVP

200 mg/m^2 of BSA per dose twice daily (the maximum dose of the immediate-release tablet formulation is NVP 200 mg twice daily) or NVP 400 mg/m^2 of BSA administered once daily as the extended-release tablet formulation (the maximum dose of the extended-release tablet formulation is NVP 400 mg once daily). For children aged ≥8 years, the recommended dose of the immediate-release tablet formulation is NVP 120 mg/m^2 of BSA per dose (with a maximum dose of NVP 200 mg) administered twice daily. The maximum dose of the extended-release tablet formulation is NVP 400 mg once daily for children aged ≥6 years.

When adjusting the dose for a growing child, the milligram dose need not be decreased (from NVP 200 mg to NVP 120 mg/m^2 of BSA) as the child reaches 8 years of age; rather, the milligram dose can be left static if no adverse effects emerge and the dose achieves the appropriate mg/m^2 of BSA dose as the child grows. Some practitioners dose NVP at 150 mg/m^2 of BSA every 12 hours or NVP 300 mg/m^2 of BSA once daily if using the extended-release tablets, regardless of age, as recommended in the FDA-approved product label. Regardless of age, the maximum dose should never exceed NVP 200 mg twice daily for immediate-release formulations of NVP or NVP 400 mg once daily for extended-release formulations of NVP.

Dosing Considerations: Lead-In Dosing

Underdosing during the lead-in period may have potentially contributed to the poorer performance of NVP in the IMPAACT P1060 trial. This potential for underdosing, which can increase the risk of resistance, has led to a re-evaluation of lead-in dosing in children who have never received NVP. Traditionally, NVP is initiated with an age-appropriate dose that is given only once daily instead of twice daily (NVP 200 mg/m^2 of BSA in infants aged ≥15 days and children aged <8 years, using the immediate-release formulations) during the first 2 weeks of treatment to allow the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in NVP metabolism.

Studies have previously indicated potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.[25] The CHAPAS-1 trial[26] randomized 211 children to initiate ART with immediate-release NVP without a lead-in dose (participants received an age-appropriate dose twice daily) or with a lead-in dose (participants received an age-appropriate dose once daily) for 2 weeks, followed by the standard twice-daily dosing of the immediate-release formulation of NVP. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and no difference emerged in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated NVP without a lead-in dose had a statistically significant increase in the incidence of Grade 2 rash, but most participants were able to continue NVP therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 count and virologic failure endpoints.

After children had been on NVP for 2 weeks, investigators conducted a substudy that examined NVP plasma concentrations 3 to 4 hours after a morning dose of NVP. Among children aged <2 years, 3 of 23 children (13%) who initiated at full dose had subtherapeutic NVP levels (<3 mg/L) at 2 weeks compared with 7 of 22 children (32%) who initiated at half dose ($P = 0.16$). No rash events occurred in the substudy group of participants aged <2 years; in the parent CHAPAS study, a strong age effect on rash occurrence was seen, with the risk of rash increasing with age. These findings suggest that a lead-in dose may not be necessary in young patients.[27]

The standard practice has been to reinitiate half-dose NVP for another 2 weeks in children who have interrupted therapy for 7 days or longer; however, given the current understanding of NVP resistance, the half-life of CYP enzymes,[28] and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends restarting full-dose NVP in children who interrupt therapy for 14 days or less.

Special Considerations for Dosing: Neonates and Premature Infants

The PK and safety of NVP during the first weeks of life were evaluated as part of IMPAACT 1115. This study demonstrated that NVP dosed at 6 mg/kg twice daily for infants ≥37 weeks gestational age (GA) and 4 mg/kg twice daily for 1 week and 6 mg/kg twice daily thereafter for infants 34 to <37 weeks GA achieved concentrations appropriate for treatment.[29] Among 438 infants (389 infants ≥37 weeks GA), measured NVP concentrations were above the minimum HIV treatment target (3 mcg/mL) in 90% of infants at Week 1 and 87% of infants at Week 2. Grade 3-4 adverse events possibly related to treatment occurred in 7% of infants (with neutropenia and anemia most common) but did not lead to NVP cessation.

PK modeling and simulation were performed with partial data from IMPAACT P1106 and P1115 to determine appropriate NVP dosing in premature infants 32 to <34 weeks GA. GA and postnatal age were significantly correlated with NVP oral clearance; thus the authors recommended a GA-based starting dose for premature infants treated with NVP and a stepwise increase in dosing at 2-week intervals.[30] These data might underestimate potential drug toxicity in infants of 32 to <34 weeks GA, because the doses used to develop the model were lower than the doses now recommended. NVP is shown to be safe in infants >34 weeks GA, so the risk of toxicity in infants 32 to <34 weeks GA seems low. The Panel considers that this risk-benefit ratio may justify the use of this dose in premature infants 32 to <34 weeks GA.

The Early Infant Treatment Study in Botswana started 40 infants with HIV ≥35 weeks GA on NVP 6 mg/kg twice daily (without lead-in dosing) along with ZDV and 3TC at a median age 2 days (range 1–5 days). NVP was switched to LPV/r at Week 2, 3, 4, or 5 according to delivery GA. Although NVP trough concentrations were below the therapeutic target (3,000 mg/mL) for 50% of 2-week measurements, 37 of 40 infants (92.5%) had an HIV RNA decline.[31] Providers who consider initiating treatment in premature infants or in infants aged <2 weeks should weigh the risks and benefits of using unapproved ART dosing and should incorporate case-specific factors, such as exposure to ARV prophylaxis.

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Rilpivirine (RPV, Edurant)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Tablets: 25 mg

Fixed-Dose Combination Tablets

- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

Co-Packaged Formulation

- [Cabenuva Kit] Cabotegravir 400 mg/2 mL (200 mg/mL) and rilpivirine 600 mg/2 mL (300 mg/mL) suspension for intramuscular injection
- [Cabenuva Kit] Cabotegravir 600 mg/3 mL (200 mg/mL) and rilpivirine 900 mg/3 mL (300 mg/mL) suspension for intramuscular injection

When using the co-packaged formulation, refer to the Cabotegravir section for additional information.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate and Infant Dose

- Rilpivirine (RPV) is not approved for use in neonates or infants.

Children Aged <12 Years

- RPV is not approved for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose

- RPV 25 mg once daily with a meal in antiretroviral therapy (ART)-naive patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to RPV and other antiretroviral (ARV) drugs in the new regimen.

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include DRESS (drug reaction [or rash] with eosinophilia and systemic symptoms).
- Hepatotoxicity
- Altered adrenocorticotropic hormone stimulation test of uncertain clinical significance

Special Instructions

- **Do not start** RPV in patients with HIV RNA >100,000 copies/mL because of the increased risk of virologic failure.
- RPV concentrations are significantly increased when either RPV or dolutegravir (DTG)/RPV is administered with a moderate- or high-fat meal.[1] Patients must be able to take RPV (or DTG/RPV) with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).

[Complera] Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (TDF)

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose

- One tablet once daily with a meal in ART-naive patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily also can be used to replace the current ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera.

[Juluca] Dolutegravir/Rilpivirine

Adult Dose

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.
- Not approved for use in children or adolescents (see the Simplification of Treatment section below).

[Odefsey] Emtricitabine/Rilpivirine/Tenofovir Alafenamide (TAF)

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose

- One tablet once daily with a meal in ART-naive patients with HIV RNA ≤100,000 copies/mL. One tablet once daily also can be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.

[Cabenuva] Cabotegravir (CAB) and Rilpivirine (RPV) Kit

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose

- Cabenuva is a two-drug co-packaged product for intramuscular (IM) injection that is approved by the U.S. Food and Drug Administration as a complete regimen for the treatment of HIV-1 in patients with HIV RNA levels <50 copies/mL on a stable ARV regimen with no history of treatment failure and no known or suspected resistance to CAB or RPV.
- Oral lead-in dosing for at least 28 days is can be used to assess tolerability prior to initiating IM CAB and RPV injections or patients can proceed directly to IM CAB and RPV on the last day of their current ARV regimen.
- Refer to Cabotegravir for dosing information.

- **Do not use** RPV with other non-nucleoside reverse transcriptase inhibitors.
- **Do not use** RPV with proton pump inhibitors (e.g., omeprazole, pantoprazole).
- Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
- H2 receptor antagonists (e.g., cimetidine, famotidine) should only be administered at least 12 hours before or at least 4 hours after RPV.
- Use RPV with caution when coadministering it with a drug that has a known risk of prolonging the QTc interval or causing Torsades de Pointes (for more information, see CredibleMeds).
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain TDF or TAF. Severe acute exacerbation of HBV infection can occur when TDF or TAF are discontinued, see Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide. Therefore, hepatic function and hepatitis B viral load should be monitored for several months after therapy with TDF or TAF is discontinued in patients with HBV.
- Refer to Cabotegravir for special instructions when using CAB and RPV for IM injection.

Metabolism/Elimination

- Cytochrome P450 3A substrate.
- Refer to Cabotegravir for information about the IM CAB and RPV regimen.

Rilpivirine Dosing in Patients with Hepatic Impairment

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Rilpivirine Dosing in Patients with Renal Impairment

- RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.
- No dose adjustment is necessary in patients with mild or moderate renal impairment. However, RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events; renal dysfunction may alter drug absorption, distribution, and metabolism, leading to increased RPV concentrations.
- The FDC tablet Complera **should not** be used in patients with creatinine clearance (CrCl) <50 mL/min, and the FDC tablet Odefsey **should not** be used in patients with CrCl <30 mL/min. Patients with CrCl <30 mL/min who are taking Juluca should be monitored closely.

• Long-acting CAB and RPV for IM injection is not approved for children aged <12 years.	• When using Complera, see the TDF section of the guidelines; when using Odefsey, see the TAF section.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate, and concentrations may be affected when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before RPV is administered.
- Coadministering RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
  - Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
  - H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV.
  - Do not use RPV with proton pump inhibitors.
- Rifampin and rifabutin significantly reduce RPV plasma concentrations; coadministration of rifampin and RPV is **contraindicated.** For patients who are concomitantly receiving rifabutin and RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal.
- In a cohort of adolescent patients, RPV exposure was two to three times greater when RPV was administered in combination with darunavir/ritonavir (DRV/r) than when RPV was administered alone.[2]

Major Toxicities

- *More common:* Insomnia, headache, rash
- *Less common (more severe):* Depression or mood changes, suicidal ideation
- In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotropic hormone (ACTH) stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, 6 out of 30 patients (20%) developed this abnormality.[3] The clinical significance of these results is unknown.
- *Rare:* RPV drug-induced liver injury has been reported.[4]

Resistance

The International Antiviral Society–USA (IAS–USA) maintains a list of updated HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Transmitted drug resistance to second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) may be present in infants and children who have recently received a diagnosis of HIV.

Pediatric Use

Approval

With the viral load and antiretroviral (ARV) resistance restrictions noted above, RPV (Edurant) used in combination with other ARV agents, the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF; Complera), the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF; Odefsey) and the long-acting injectable regimen of cabotegravir (CAB) and RPV (Cabenuva) are all approved by the U.S. Food and Drug Administration (FDA) for use in persons aged ≥12 years and weighing ≥35 kg. The FDC tablet dolutegravir/rilpivirine (DTG/RPV; Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.

Efficacy in Clinical Trials

An RPV-containing regimen has been compared to an efavirenz (EFV)-containing regimen in two large clinical trials in adults—ECHO and THRIVE. In both studies, RPV was shown to be non-inferior to EFV. Patients with pretreatment HIV viral loads ≥100,000 copies/mL who received RPV had higher rates of virologic failure than those who received EFV. These findings resulted in FDA approval for initial therapy with RPV only in patients with HIV viral loads ≤100,000 copies/mL.[5-8]

A study of antiretroviral therapy (ART)-naive adolescents aged 12 to 18 years demonstrated that RPV 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. In studies of adolescents with baseline viral loads ≤100,000 copies/mL, 86% had a virologic response at 24 weeks and 79% had a virologic response at 48 weeks. In adolescents with baseline viral loads >100,000 copies/mL, 38% had a virologic response at 24 weeks and 50% had a virologic response at 48 weeks.[9]

Patients must be able to take RPV on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation Odefsey is a small pill and can be useful for certain patients who have difficulty swallowing pills and want to switch from a multipill regimen, and who do not have any drug resistance mutations that are associated with the components of Odefsey.

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years) who acquired HIV perinatally to receive FTC/RPV/TDF (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, 4 were on an NNRTI-based regimen, and 1 had not received ART. After a median follow-up of 90 weeks (for participants with undetectable viral loads at baseline) or 40 weeks (for participants with detectable viral loads at baseline), 86% and 89% of patients, respectively, achieved and maintained an undetectable viral load. None of the patients discontinued RPV-based therapy because of adverse events (AEs); no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved, and two adolescents with a history of insomnia and abnormal dreams while receiving EFV-based therapy did not report similar problems while receiving RPV-based therapy.[10]

Pharmacokinetics

The pharmacokinetics (PKs), safety, and efficacy of RPV in children aged <12 years have not been established but are currently being studied in patients aged 6 years to <12 years and weighing ≥17 kg (*ClinicalTrials.gov* identifier NCT00799864). The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has agreed that the use of RPV may be appropriate in certain children aged <12 years and weighing ≥35 kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to prescribing RPV for a child in this age and weight group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, Pediatric Study in Adolescents Investigating a New NNRTI TMC278 (PAINT), investigated a 25-mg dose of RPV given in combination with two NRTIs in ARV-naive adolescents aged 12 years to <18 years who weighed ≥32 kg and who had viral loads ≤100,000 copies/mL.[9] In the dose-finding phase of the study, 11 youth aged >12 years to ≤15 years and 12 youth aged >15 years to ≤18 years underwent intensive PK assessment after they took an observed dose of RPV with a meal. PKs were comparable to those in adults; results are listed in the table below.[11]

Table A. Rilpivirine Pharmacokinetics in Adults and Adolescents Aged 12 Years to <18 Years

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Dose	RPV 25 mg once daily	RPV 25 mg once daily
Number of Participants Studied	679	34
AUC_{24h} (ng·h/mL)		
Mean ± SD	2,235 ± 851	2,424 ± 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
C_{0h} (ng/mL)		
Mean ± SD	79 ± 35	85 ± 40
Median (Range)	73 (2–288)	79 (7–202)

Source: Adapted from Rilpivirine [package insert]. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202022s014lbl.pdf [12]

Key: AUC_{24h} = area under the curve after 24 hours; C_{0h} = plasma concentration just prior to next dose; RPV = rilpivirine; SD = standard deviation

In a PK study of youth aged 13 to 23 years who received RPV,[2] RPV exposure was comparable to the exposure observed during the PAINT study in patients who received 25-mg doses of RPV without DRV/r and substantially higher than the exposure observed in those who received 25-mg doses of RPV with DRV/r (RPV area under the curve in this study was 6,740 ng·h/mL). No dose adjustments are currently recommended for adults when RPV is coadministered with DRV/r, where a similar twofold to threefold increase in RPV exposure has been reported.[3]

RPV has been reported to have fewer CNS AEs than EFV, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving EFV. However, concern exists that the prolonged half-life of EFV might result in residual drug levels that could have an impact on RPV levels. A Thai study evaluated 20 Thai adolescents 4 weeks after they switched from EFV to RPV. The PK parameters of RPV in this study population were comparable to those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks, and no patients discontinued RPV because of AEs.[13]

Simplification of Treatment

Juluca is an FDC tablet that contains DTG 50 mg and RPV 25 mg. The results from two trials in adults (SWORD-1 and SWORD-2) supported FDA approval of DTG/RPV as a complete regimen for treatment simplification or maintenance therapy in certain patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations that are associated with DTG or RPV. The participants were randomized to receive DTG/RPV ("early switch") or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.[14] After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV ("late switch"). At 148 weeks of treatment, 84% of the early switch patients and 90% of the late switch patients remained virologically suppressed, and only 11 patients receiving dual therapy (DTG/RPV) met virologic failure criteria. No integrase inhibitor resistance was identified.[15] More AEs were reported, and more AEs led to treatment discontinuation in the DTG/RPV arm during the comparative randomized phase. In a subgroup of SWORD study patients whose original ARV regimen contained TDF, small but statistically significant increases in hip and spine bone mineral density were observed.[16] Although DTG/RPV as Juluca is not approved for use in adolescents, the doses of both component drugs that make up Juluca are approved for use in adolescents. This product may be appropriate for certain adolescents; however, because the strategy of treatment simplification has not been evaluated in adolescents, who may have difficulties adhering to therapy, the Panel **does not recommend** using Juluca in adolescents and children until more data are available.

Long-Acting Injectable Rilpivirine

A long-acting injectable formulation of RPV has recently been approved for coadministration with long-acting injectable CAB as a complete ARV regimen for children and adolescents aged ≥ 12 years and weighing ≥35 kg and adults with HIV RNA levels <50 copies/mL, on a stable ARV regimen, with no history of treatment failure, and no known or suspected resistance to CAB or RPV.[17] This formulation has been evaluated in adults as monthly or every-2 month intramuscular injections following an initial oral, lead-in daily dose for 4 weeks to assess toxicity.[18-20] These studies in adult patients demonstrated non-inferior efficacy to standard oral therapy and good participant satisfaction and tolerability through 96 weeks. A follow-on study demonstrated that dosing IM CAB and RPV every 2 months in virally suppressed participants provided similar safety and efficacy to monthly injections through 48 weeks.[21] IMPAACT study 2017, More Options for Children and Adolescents (MOCHA), is currently evaluating the safety, tolerability, acceptability, and PK profile of this injectable regimen in adolescents weighing ≥35 kg (*ClinicalTrials.gov* identifier NCT03497676). See the Cabotegravir section for more information about this regimen.

Toxicity

In the PAINT study, the observed AEs were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, headache). The incidence of depressive disorders was

19.4% (7 of 36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grade 3 and 4 depressive disorders was 5.6% (2 of 36 participants). [3]

Six out of 30 adolescents (20%) with a normal ACTH stimulation test at baseline developed an abnormal test during the trial. No serious AEs, deaths, or treatment discontinuations were attributed to adrenal insufficiency. The clinical significance of abnormal ACTH stimulation tests is not known, but this finding warrants further evaluation. [3]

Crushing Tablets for Enteral Administration

Some cases report DTG/RPV tablets' being crushed and successfully administered via an enteral tube.[22] If DTG/RPV is administered via enteral tube, care should be taken to disperse the tablets completely and flush the tube to avoid clogging.

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Protease Inhibitors (PIs)

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Atazanavir (ATV, Reyataz)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Powder Packet: 50 mg/packet

Capsules: 150 mg, 200 mg, 300 mg

Generic Formulations

- 150 mg, 200 mg, and 300 mg capsules

Fixed-Dose Combination Tablets

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg

Capsules and powder packets are not interchangeable.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate Dose

- Atazanavir (ATV) is not approved for use in neonates and infants aged <3 months. ATV **should not be administered** to neonates because of risks associated with hyperbilirubinemia (e.g., bilirubin-induced neurologic dysfunction).

Infant and Child Dose

Powder Formulation of Atazanavir[a]

- The powder formulation of ATV must be administered with ritonavir (RTV).
- The powder formulation is not approved for use in infants aged <3 months or weighing <5 kg.

Atazanavir Powder Dosing Table for Infants and Children Aged ≥3 Months and Weighing ≥5 kg[a]

Weight	Once-Daily Dose
5 kg to <15 kg	ATV 200 mg (four packets) plus RTV 80 mg (1 mL oral solution) with food
15 kg to <25 kg[b]	ATV 250 mg (five packets) plus RTV 80 mg (1 mL oral solution) with food

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Nephrolithiasis
- Increased serum transaminases
- Hyperlipidemia (occurs primarily with RTV boosting)

Special Instructions

- Administer ATV with food to enhance absorption.
- Capsules and powder packets **are not interchangeable.**
- Do not open capsules.
- Because ATV can prolong the PR interval of the electrocardiogram, use ATV with caution in patients with preexisting cardiac conduction system disease or with other drugs that are known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the ATV package insert).

Capsule Formulation of Atazanavir[a]

- ATV capsules are not approved for use in children aged <6 years or weighing <15 kg.

Atazanavir/Ritonavir Capsule Dosing Table for Children and Adolescents Aged ≥6 Years and Weighing ≥15 kg

Weight	Once-Daily Dose
<15 kg	Capsules not recommended
15 kg to <35 kg	ATV/r 200 mg/100 mg, both with food[c]
≥35 kg	ATV/r 300 mg/100 mg, both with food[c]

ART-Naive Patients Who Are Unable to Tolerate Ritonavir

Child and Adolescent (Aged ≥13 Years and Weighing ≥40 kg) and Adult Dose

- ATV 400 mg (capsule formulation only) once daily with food
- ATV powder is not an option, because it must be administered with RTV.
- For the capsule formulation, although the U.S. Food and Drug Administration (FDA) does not recommend the use of unboosted ATV in children aged <13 years, adolescents aged ≥13 years and weighing ≥40 kg may be prescribed unboosted ATV if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).
- To achieve target drug concentrations, adolescents may require doses of ATV that are higher than those recommended for use in adults (see Pediatric Use below).
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **does not recommend** the use of unboosted ATV.

ART-Naive and ART-Experienced Patients

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- Atazanavir/ritonavir (ATV/r) 300 mg/100 mg once daily with food[d]
- Atazanavir/cobicistat (ATV/c) 300 mg/150 mg once daily with food, administered as single agents simultaneously or as the coformulated drug Evotaz.[e]
- Both ATV/r and ATV/c must be used in combination with other antiretroviral drugs.

[Evotaz] Atazanavir/Cobicistat

Child and Adolescent (Weighing ≥35 kg) and Adult Dose

- One tablet once daily with food

- The plasma concentration and, therefore, the therapeutic effect of ATV can be expected to decrease substantially when ATV is coadministered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients who are receiving any PPI should receive a dose of that PPI that is equivalent to no more than a 20-mg dose of omeprazole. PPIs should be taken approximately 12 hours before taking boosted ATV. Coadministration of ATV with PPIs **is not recommended** in ART-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients who had marked elevations in transaminase levels before treatment may have an increased risk of further elevations in transaminase levels or hepatic decompensation.
- ATV oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet of oral powder contains 35 mg of phenylalanine.

Powder Administration

- Mix ATV oral powder with at least 1 tablespoon of soft food (e.g., applesauce, yogurt). Oral powder mixed with a beverage (at least 30 mL of milk or water) may be used for older infants who can drink from a cup. For young infants (aged <6 months) who cannot eat solid food or drink from a cup, oral powder should be mixed with at least 10 mL of infant formula and administered using an oral dosing syringe.
- Administer RTV immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.

Metabolism/Elimination

- ATV is a substrate and inhibitor of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase 1A1.

Atazanavir Dosing in Patients with Hepatic Impairment

- ATV should be used with caution in patients with mild or moderate hepatic impairment. Consult the manufacturer's prescribing information for the dose adjustment in patients with moderate impairment.
- ATV **should not be used** in patients with severe hepatic impairment.

Atazanavir Dosing in Patients with Renal Impairment

- No dose adjustment is required for patients with renal impairment.

	• ATV should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.

[a] mg/kg dosing is higher for the ATV powder packets than for the capsules. In P1020A, children of similar age and size who were taking ATV powder had lower exposures than those who were taking ATV capsules.

[b] Children weighing ≥25 kg who cannot swallow ATV capsules may receive ATV 300 mg oral powder (six packets) plus RTV 100 mg oral solution, both administered once daily with food.

[c] Either RTV capsules or RTV oral solution can be used.

[d] Adult patients who cannot swallow capsules may take ATV oral powder once daily with food using the adult dose for the capsules. ATV oral powder should be administered with RTV.

[e] See the Cobicistat section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat (COBI) and the combination of COBI and TDF.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Atazanavir (ATV) is both a substrate and an inhibitor of the cytochrome P450 (CYP) 3A4 enzyme system and has significant interactions with drugs that are highly dependent on CYP3A4 for metabolism. ATV also competitively inhibits CYP1A2 and CYP2C9. ATV is a weak inhibitor of CYP2C8. ATV inhibits the glucuronidation enzyme uridine diphosphate glucuronosyl transferase (UGT1A1). Because of the potential for multiple drug interactions with ATV, a patient's medication profile should be carefully reviewed for potential drug interactions before administering ATV.
- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir disoproxil fumarate (TDF) decreases ATV plasma concentrations. Only atazanavir/ritonavir (ATV/r) or atazanavir/cobicistat (ATV/c) should be used in combination with TDF. The effect of tenofovir alafenamide (TAF) on unboosted ATV is unknown; thus, only ATV/r or ATV/c should be used with TAF.
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz (EFV), etravirine (ETR), and nevirapine (NVP) decrease ATV plasma concentrations significantly. NVP and ETR **should not be administered** to patients who are receiving ATV (with or without a booster). Although the combination of EFV and ATV/r is not commonly used in clinical practice, EFV may be used in combination with ritonavir (RTV)-boosted ATV 400 mg in antiretroviral therapy (ART)-naive patients. ATV/r should be taken with food, and EFV should be taken on an empty stomach, preferably at bedtime. Coadministering ATV/r and EFV in ART-experienced patients **is not recommended,** because this combination is expected to result in suboptimal ATV exposure in these patients.
- *Integrase strand transfer inhibitors:* ATV is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir (RAL). This interaction may not be clinically significant.
- *Absorption:* ATV absorption is dependent on low gastric pH. The dose for ATV should be adjusted when it is administered with medications that alter gastric pH. Guidelines for the appropriate doses of ATV to use with antacids, H2 receptor antagonists, and proton-pump inhibitors in adults are complex and can be found in the package insert for ATV. No information is available on the appropriate doses of ATV to use in children when the drug is coadministered with medications that alter gastric pH.

- Coadministering cobicistat (COBI)—a CYP3A4 inhibitor—and medications that are metabolized by CYP3A4 may increase the plasma concentrations of these medications. This may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions) that are associated with the concomitant medications. Coadministration of COBI, ATV, and CYP3A4 inducers may lead to lower exposures of COBI and ATV, a loss of efficacy of ATV, and possible development of resistance.[1] Coadministering COBI and ATV with some antiretroviral (ARV) agents (e.g., with ETR, with EFV in ART-experienced patients, or with another ARV drug that requires pharmacokinetic [PK] enhancement, such as another protease inhibitor [PI] or elvitegravir) may result in decreased plasma concentrations of that agent, leading to loss of therapeutic effect and the development of resistance.

Major Toxicities

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesia.
- *Less common:* Prolongation of the electrocardiogram PR interval. Abnormalities in atrioventricular (AV) conduction are generally limited to first-degree AV block, but second-degree AV block has been reported. Rash is generally mild or moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. The use of ATV/r is associated with lipid abnormalities, but to a lesser extent than with other boosted PIs.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Chronic kidney disease, including biopsy-proven cases of granulomatous interstitial nephritis that were associated with the deposition of ATV drug crystals in the renal parenchyma have occurred. Nephrolithiasis and cholelithiasis have been reported. Hepatotoxicity (patients with hepatitis B virus or hepatitis C virus infections are at increased risk of hepatotoxicity).

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

ATV is approved by the U.S. Food and Drug Administration (FDA) for use in infants (aged ≥3 months and weighing ≥5 kg), children, and adolescents. ATV coformulated with COBI (as Evotaz) has been approved by the FDA for use in pediatric patients weighing ≥35 kg.

Efficacy

Studies in ART-naive adults have shown that ATV/r is as effective as EFV and lopinavir/ritonavir (LPV/r) when these drugs are administered with two NRTIs.[2-5] In AIDS Clinical Trials Group (ACTG) A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or RAL, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, the regimen that contained ATV/r was discontinued more frequently than the other regimens because of toxicity but most often because of hyperbilirubinemia or gastrointestinal complaints.[6]

International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT)/Pediatric AIDS Clinical Trials Group (PACTG) P1020 enrolled 195 ART-naive and ART-experienced patients with HIV aged 3 months to 21 years. Capsule and powder formulations of ATV given with and without RTV boosting were investigated in this open-label study; area under the curve (AUC) targeting was used to direct dose finding. Of the 195 patients enrolled, 142 patients received ATV-based treatment at the final recommended dose. Among these patients, 58% were ART-naive. At Week 48, 69.5% of the ART-naive patients and 43.3% of the ART-experienced patients had HIV viral loads ≤400 copies/mL.[7,8]

Two open-label clinical trials in infants and children, PRINCE-1 and PRINCE-2, studied a powder formulation of ATV that was administered once daily and boosted with liquid RTV.[9-11] In total, 134 infants and children aged ≥3 months and weighing between 5 kg and 35 kg were evaluated. Using a modified intent-to-treat analysis, 28 of 52 ARV-naive patients (54%) and 41 of 82 ART-experienced patients (50%) had HIV RNA <50 copies/mL at Week 48. The median increase from baseline in absolute CD4 T lymphocyte cell count at 48 weeks of therapy was 215 cells/mm^3 (a 6% increase) in ARV-naive patients and 133 cells/mm^3 (a 4% increase) in ARV-experienced patients.

Pharmacokinetics and Dosing

Oral Capsule

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of RTV boosting, ATV can achieve protocol-defined PK targets—but only when used at higher doses (on a mg per kg body weight or mg per m^2 of body surface area basis) than the doses that are currently recommended in adults. In IMPAACT/PACTG 1020A, children aged >6 years to <13 years required a dose of 520 mg per m^2 of body surface area per day of the ATV capsule formulation to achieve PK targets.[8] Unboosted ATV at this dose was well tolerated in those aged <13 years who were able to swallow capsules.[12] The approved dose for adults is ATV 400 mg once daily without RTV boosting; however, adolescents aged >13 years required a dose of ATV 620 mg per m^2 of body surface area per day.[8] In this study, the AUCs for the unboosted arms were similar to those seen in the ATV/r arms, but the maximum plasma concentration (C_{max}) was higher and the minimum plasma concentration (C_{min}) was lower in the unboosted arms. Median doses of ATV, both with and without RTV boosting, from IMPAACT/PACTG 1020A are outlined in the table below. When administering unboosted ATV to pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate ATV plasma concentrations have been achieved. A minimum target trough concentration for ATV is 150 mg/mL.[13] Higher target trough concentrations may be required in PI-experienced patients. IMPAACT P1058, a study of unboosted ATV PKs in ART-experienced children, concluded that once-daily ATV 400 mg provided suboptimal exposure and that administering higher, unboosted doses or splitting the daily dose into twice-daily doses warranted investigation in ART-experienced children, adolescents, and young adults.[14]

Table A. Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A

Age Range	ATV Given with RTV	ATV Median Dose (mg/m²)[a]	ATV Median Dose (mg)
6–13 years	No	509	475
6–13 years	Yes	206	200
>13 years	No	620	900
>13 years	Yes	195	350

[a] These doses satisfied protocol-defined area under the curve/pharmacokinetic parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. Therapeutic drug monitoring was used to determine patient-specific dosing in this trial.

Source: Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-96.

Key: ATV = atazanavir; RTV = ritonavir

In the report of the IMPAACT/PACTG P1020A data, ATV satisfied PK criteria at a dose of 205 mg per m^2 of body surface area in pediatric subjects when administered with RTV.[12] A study of a model-based approach that used ATV concentration-time data from three adult studies and one pediatric study (P1020A),[15] along with subsequent additional adjusted modeling,[16] informed the use of the following weight-based ATV/r doses that are listed in the current FDA-approved product label for children aged ≥6 years to <18 years:

- Weighing 15 kg to <35 kg: ATV/r 200 mg/100 mg
- Weighing ≥35 kg: ATV/r 300 mg/100 mg

Cobicistat as a Pharmacokinetic Enhancer

COBI (as Tybost) is approved by the FDA at the 150-mg dose for use with ATV 300 mg in children and adolescents weighing ≥35 kg. A study of 14 adolescents, aged 12 to 18 years, showed that COBI is a safe and effective PK enhancer when used in combination with ATV and two NRTIs in adolescent patients.[17] PK findings from this study are summarized in Table B below.

Table B. Pharmacokinetic Parameters for Atazanavir Administered with Cobicistat (as Tybost) in Pediatric Patients Aged 12 to 18 Years and Adults

PK Parameters[a]	ATV		COBI	
	Pediatric Patients (n = 12)	Adult Patients (n = 30)	Pediatric Patients (n = 12)	Adult Patients (n = 30)
AUC_{tau} µg·h/mL Geometric mean (CV%)	49.48 (49.1)	39.96 (52.1)	12.11 (44.7)	9.65 (41.8)
C_{max} µg/mL Geometric mean (CV%)	4.32 (49.9)	3.54 (45.8)	1.28 (31.7)	1.28 (35.6)
C_{tau} µg/mL Geometric mean (CV%)	0.91 (96.4)	0.58 (84.7)	0.09 (156.2)	0.04 (112.7)

[a] The information in this table comes from the Tybost package insert.[10]

Key: ATV = atazanavir; AUC_{tau} = area under the concentration time curve over the dosing interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; COBI = cobicistat; CV = coefficient of variation; PK = pharmacokinetic

Oral Powder

The unboosted ATV powder arms in IMPAACT/PACTG P1020A were closed, because participants were unable to achieve target exposures. For the IMPAACT/PACTG P1020A trial, AUC targets (30,000 ng·hr/mL to 90,000 ng·hr/mL) were established based on exposures in adults in early studies of unboosted ATV. In IMPAACT/PACTG P1020A, children aged 3 months to 2 years who were in the boosted ATV powder cohorts and who received a daily dose of ATV 310 mg per m^2 of body surface area achieved average ATV exposures that approached, but did not meet, protocol targets. Variability in exposures was high, especially among the very young children of 3 months to 2 years in this study.[8]

Assessment of the PKs, safety, tolerability, and virologic response of ATV oral powder for FDA approval was based on data from two open-label, multicenter clinical trials:

- PRINCE-1, which enrolled pediatric patients aged 3 months to <6 years;[9] and
- PRINCE-2, which enrolled pediatric patients aged 3 months to <11 years.[10]

In total, 134 treated patients (weighing 5 kg to <35 kg) from both studies were evaluated during the FDA approval process. All patients in the PRINCE trials were treated with boosted ATV and two NRTIs. Children received an oral solution that contained ATV and RTV. Doses were assigned according to the child’s weight:

- Weighing 5 kg to <10 kg: ATV 150 mg or ATV 200 mg and RTV 80 mg
- Weighing 10 kg to <15 kg: ATV 200 mg and RTV 80 mg
- Weighing 15 kg to <25 kg: ATV 250 mg and RTV 80 mg
- Weighing 25 kg to <35 kg: ATV 300 mg and RTV 100 mg

No new safety concerns were identified during these trials. Table C lists the PK parameters that were measured during the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses.

Table C. Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE-1 and PRINCE-2) versus Capsules in Young Adults and Adults

PK Parameters	PRINCE Trial[a] ATV/r					Young Adult Study[b]	Adult Study
	Dose: 150 mg/ 80 mg Weighing: 5 kg to <10 kg	Dose: 200 mg/ 80 mg Weighing: 5 kg to <10 kg	Dose: 200 mg/ 80 mg Weighing: 10 kg to <15 kg	Dose: 250 mg/ 80 mg Weighing: 15 kg to <25 kg	Dose: 300 mg/ 100 mg Weighing: ≥25 kg to <35 kg		
AUC ng·h/mL Mean[c] (CV% or 95% CI)	32,503 (61) n = 20	39,519 (54) n = 10	50,305 (67) n = 18	55,687 (45) n = 31	44,329 (63) n = 8	35,971 (30,853–41,898) n =22	46,073 (66) n =10
C_{24h} ng/mL Mean[c] (CV% or 95% CI)	336 (76) n = 20	550 (60) n = 10	572 (111) n = 18	686 (68) n = 31	468 (104) n = 8	578 (474–704) n = 22	636 (97) n = 10

[a] This information comes from the Reyataz package insert.[10]

[b] The young adults also were receiving tenofovir disoproxil fumarate.[7]

[c] Means are geometric means.

Key: ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation; PK = pharmacokinetic

In these PK studies, although the PK targets were met in all patients using ATV powder except those who received ATV/r 150 mg/80 mg in the 5 kg to <10 kg weight band, the coefficients of variation were large, especially among the youngest patients.

Transitioning from Powder to Capsules

For children who reach a weight ≥25 kg while taking the powder, ATV 300 mg powder (six packets) plus RTV 100 mg oral solution, both administered once daily with food, may be used. ATV capsules should be used for children who can swallow pills. Bioavailability is higher for the capsules than for the powder; therefore, a lower mg/kg dose is recommended when using capsules. Opened capsules have not been studied and should not be used.

Toxicity

In the IMPAACT/PACTG 1020A trial, 9% of patients enrolled had a total bilirubin ≥5.1 times the upper limit of normal,[12] whereas 9% of patients enrolled in the PRINCE studies had a total bilirubin ≥2.6 times the upper limit of normal.[9,11] The most common laboratory abnormality during the PRINCE trials was elevated amylase levels, which occurred in 33% of patients.[10] Three children (2%) had treatment-related cardiac disorders during the PRINCE trials; one child discontinued therapy because of QT corrected for heart rate (QTc) prolongation, and two experienced first-degree AV block.[9,11] In IMPAACT/PACTG P1020A, three children (3%) had QTc prolongations >470 msec; two of these children came off the study, and all were asymptomatic.

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Darunavir (DRV, Prezista)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Oral Suspension: 100 mg/mL **Tablets:** 75 mg, 150 mg, 600 mg, 800 mg **Fixed-Dose Combination (FDC) Tablets** • [Prezcobix] Darunavir 800 mg/cobicistat 150 mg • [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Note: Darunavir (DRV) should not be used without a pharmacokinetic enhancer (boosting agent). Ritonavir (RTV) may be used as the boosting agent in children and adults. Cobicistat (COBI) may be used as a boosting agent with DRV in children weighing ≥40 kg and in adults. **Neonate/Infant Dose** • DRV is not approved for use in neonates/infants. **Child Dose** *Aged <3 Years* • **Do not use DRV in children aged <3 years or weighing ≤10 kg.** In juvenile rats, DRV caused convulsions and death; these events have been attributed to immaturity of the blood–brain barrier and liver metabolic pathways. *Aged ≥3 Years to <12 Years* • Dosing recommendations in the table below are for children aged ≥3 years to <12 years and weighing ≥10 kg who are antiretroviral therapy–naive or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with DRV resistance.	• Skin rash, including Stevens-Johnson syndrome and erythema multiforme • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia, transaminase elevation, hyperglycemia • Fat maldistribution **Special Instructions** • Once-daily DRV is not generally recommended for use in children aged <12 years or weighing <40 kg. Dosing estimates for these patients were based on limited data, and limited clinical experience exists with this dosing schedule in this age group. • Once-daily DRV **should not be used** if any one of the following resistance-associated mutations is present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V. • **DRV must be administered with food,** which increases DRV plasma concentrations by about 30%. • DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies. • Pediatric dosing requires coadministration of tablets of different strengths to achieve the recommended dose for each weight band. It is important to provide careful

Twice-Daily Darunavir and Ritonavir Doses for Children Aged 3 Years to <12 Years and Weighing ≥10 kg

Weight	Dose (Twice Daily with Food)[a]
10 kg to <11 kg[b]	DRV 200 mg (2.0 mL) plus RTV 32 mg (0.4 mL)
11 kg to <12 kg[b]	DRV 220 mg (2.2 mL) plus RTV 32 mg (0.4 mL)[c]
12 kg to <13 kg[b]	DRV 240 mg (2.4 mL) plus RTV 40 mg (0.5 mL)[c]
13 kg to <14 kg[b]	DRV 260 mg (2.6 mL) plus RTV 40 mg (0.5 mL)[c]
14 kg to <15 kg	DRV 280 mg (2.8 mL) plus RTV 48 mg (0.6 mL)[c]
15 kg to <30 kg	DRV 375 mg (combination of tablets or 3.8 mL)[d] plus RTV 48 mg (0.6 mL)[d]
30 kg to <40 kg	DRV 450 mg (combination of tablets or 4.6 mL)[d,e] plus RTV (100 mg tablet or powder or 1.25 mL)[b]
≥40 kg	DRV 600 mg (tablet or 6 mL) plus RTV 100 mg (tablet or 1.25 mL)

Child and Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients with or Without at Least One Mutation Associated with Darunavir Resistance

- DRV 450 mg (using a combination of tablets) plus RTV 100 mg, both **twice daily with food**

Child and Adolescent (Aged ≥12 years and Weighing ≥40 kg)[e] and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance

- DRV 800 mg (using a tablet or combination of tablets) plus RTV 100 mg, both **once daily with food**

Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance

- DRV 800 mg (tablet) plus COBI[f] 150 mg (tablet) or the coformulation Prezcobix, **once daily with food**

Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Experienced Patients with at Least One Mutation Associated with Darunavir Resistance

- DRV 600 mg plus RTV 100 mg, both **twice daily with food**

instructions to caregivers when recommending a combination of different-strength tablets.

- Store DRV tablets and oral suspension at room temperature (25ºC or 77ºF). The suspension must be shaken well before dosing.
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain emtricitabine (FTC) or tenofovir alafenamide (TAF). Severe acute exacerbation of HBV infection can occur when FTC or TAF are discontinued; therefore, liver function should be monitored for several months after patients with HBV infection stop taking FTC or TAF.

Metabolism/Elimination

- Cytochrome P450 3A4 substrate and inhibitor

Darunavir Dosing in Patients with Hepatic Impairment

- DRV is primarily metabolized by the liver. Caution should be used when administering DRV to patients with hepatic impairment. DRV **is not recommended** in patients with severe hepatic impairment.

Darunavir Dosing in Patients with Renal Impairment

- No DRV dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30–60 mL/min).
- The FDC Symtuza **is not recommended** for use in patients with an estimated creatinine clearance <30 mL/min.

• The use of COBI **is not recommended** with DRV 600 mg twice daily. **[Prezcobix] Darunavir/Cobicistat** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance* • One tablet once daily with food **[Symtuza] Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose* • One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no known mutations associated with resistance to DRV or tenofovir.	

[a] Once-daily dosing of DRV is approved by the U.S. Food and Drug Administration (FDA), but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not generally recommend using this dosing schedule in children (see Frequency of Administration below).

[b] Note that the dose in children weighing 10 kg to 15 kg is DRV 20 mg/kg plus RTV 3 mg/kg of body weight per dose, which is higher than the weight-adjusted dose in children with higher body weights.

[c] RTV 80 g/mL oral solution.

[d] The volumes for the 375-mg and 450-mg DRV doses are rounded for suspension-dose convenience.

[e] Some Panel members recommend using the FDA-approved dose of once-daily DRV 675 mg (administered using a combination of tablets) plus RTV 100 mg once daily for adolescents weighing ≥30 kg to <40 kg (see Table B below).

[f] See the Cobicistat section for important information about toxicity, drug interactions, and monitoring in patients who receive COBI.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Darunavir (DRV) is primarily metabolized by cytochrome P450 (CYP) 3A4. Both ritonavir (RTV) and cobicistat (COBI) are inhibitors of CYP3A4, thereby increasing the plasma concentration of DRV. Coadministration of DRV plus RTV (DRV/r) or DRV plus COBI (DRV/c) with drugs that are highly dependent on CYP3A clearance creates potential for multiple drug–drug interactions and may be associated with suboptimal efficacy or serious and/or life-threatening events.

- Coadministration of several drugs, including other protease inhibitors and rifampin, is **contraindicated** with DRV/r and DRV/c. A study involving adults with HIV suggested that etravirine (ETR) may reduce serum DRV concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent.[1] Before administering DRV with a pharmacokinetic (PK) enhancer (boosting agent), a patient's medication profile should be carefully reviewed for potential drug interactions.

- When twice-daily DRV/r was used in combination with tenofovir disoproxil fumarate (TDF) in 13 patients with HIV aged 13 to 16 years, both TDF and DRV exposures were lower than those found in adults treated with the same combination.[2] No dose adjustment is recommended when using DRV/r with TDF, but caution is advised and therapeutic drug monitoring (TDM) may be useful. Data from the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) protocol P1058A indicate that coadministering once-daily DRV/r with once-daily or twice-daily ETR in children, adolescents, and young adults aged 9 years to <24 years did not have a significant effect on DRV plasma concentrations.[3] When DRV/r was coadministered with ETR twice daily in pediatric patients, target concentrations for both DRV and ETR were achieved.[4] DRV PKs were not affected when DRV was coadministered with rilpivirine (RPV) in a study of adolescents and young adults.[5] DRV/r coadministration increased RPV exposure twofold to threefold; close monitoring for RPV-related adverse events is advisable.

Major Toxicities

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- *Less common:* Skin rash, including erythema multiforme and Stevens-Johnson syndrome, fever and elevated levels of hepatic transaminases, lipid abnormalities, and crystalluria.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors, such as hepatitis B or hepatitis C virus coinfection.

Resistance

The International Antiviral Society–USA maintains a list of updated HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

DRV/r is approved by the U.S. Food and Drug Administration (FDA) as a component of antiretroviral (ARV) therapy in treatment-naive and treatment-experienced children aged ≥3 years.

DRV is approved by the FDA to be administered with COBI (Tybost) boosting in pediatric patients weighing ≥40 kg. The fixed-dose combinations (FDCs) DRV/c (Prezcobix) and Symtuza (DRV/c/emtricitabine/tenofovir alafenamide) are also approved by the FDA for use in pediatric patients weighing ≥40 kg.

Efficacy in Clinical Trials

In an international, multisite clinical trial (TMC114-TiDP29-C228) that enrolled treatment-experienced children aged 3 years to <6 years, 17 (81%) of 21 children who received DRV/r twice daily had viral loads <50 copies/mL at Week 48.[6-8]

A randomized, open-label, multicenter pediatric trial[8] that evaluated twice-daily DRV/r among 80 treatment-experienced children aged 6 years to <18 years reported that 66% of patients had plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL at Week 24.

Once-daily DRV/r has been investigated in a small study involving 12 treatment-experienced children aged 6 to 12 years who had maintained HIV viral loads <50 copies/mL for at least 6 months.[9] All but one child continued to have undetectable viral loads during a median of 11.6 months of follow-up (range 0.5–14.2 months). The remaining child had detectable viral load measurements between 20 copies/mL and 200 copies/mL on three occasions during a 3-month period before, again, becoming undetectable without a change in regimen.

In one study, 12 participants aged 12 to 17 years received DRV/r once daily.[10] After 48 weeks, all but one participant had viral loads <50 copies/mL.

Pharmacokinetics and Dosing

Pharmacokinetics in Children Aged 3 Years to <6 Years

Twenty-one children aged 3 years to <6 years and weighing 10 kg to <20 kg received twice-daily DRV/r oral suspension. These children had experienced virologic failure on their previous ARV regimens and had fewer than three DRV resistance mutations, confirmed by genotypic testing.[6,7,11] The DRV area under the curve ($AUC_{0–12h}$), measured as a percent of the adult AUC value,[6,7,11] was 128% overall: 140% in children weighing 10 kg to <15 kg and 122% in children weighing 15 kg to <20 kg.

Pharmacokinetics in Children Aged >6 Years

Initial pediatric PK evaluation of DRV tablets and RTV oral solution or tablets was based on a Phase 2 randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 years to <18 years and weighing ≥20 kg.[12] Part 1 of the trial used a weight-adjusted dose of DRV (9 mg/kg to 15 mg/kg) and RTV (1.5 mg/kg to 2.5 mg/kg) twice daily, approximating the standard adult dose of DRV/r 600 mg/100 mg twice daily on a per-weight basis. This dose resulted in inadequate drug exposure in the pediatric population studied, with a 24-hour AUC (AUC_{24h}) that was 81% of the AUC_{24h} observed in adults and a pre-dose concentration (C_{0h}) that was 91% of the C_{0h} observed in adults. A pediatric dose that was 20% to 33% higher than the directly scaled adult dose was needed to achieve a drug exposure that was similar to that found in adults, and this was the dose selected for Part 2 of the study. The higher dose used for the safety and efficacy evaluation was DRV 11 mg/kg to 19 mg/kg and RTV 1.5 mg/kg to 2.5 mg/kg twice daily. This dose resulted in a DRV AUC_{24h} of 123.3 mcg·h/mL (range 71.9–201.5 mcg·h/mL) and a C_{0h} of 3,693 ng/mL (range 1,842–7,191 ng/mL), representing 102% and 114% of the respective values in adults. Doses were given twice daily and were stratified into body-weight bands of 20 kg to <30 kg and 30 kg to <40 kg. The current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 kg to <40 kg were selected using the findings from the safety and efficacy portion of this study (see Table A below).

A small study that involved 12 treatment-experienced children aged 6 to 12 years examined the PKs and efficacy of DRV/r once daily administered in combination with abacavir and lamivudine.[9] All participants had maintained HIV plasma viral loads <50 copies/mL for at least 6 months prior to beginning this regimen. The weight-based doses used for once-daily DRV/r were based on a prior modeling study:[13] 600 mg/100 mg for patients weighing 15 kg to 30 kg, 675 mg/100 mg for patients weighing 30 kg to 40 kg, and 800 mg/100 mg for patients weighing >40 kg. The geometric mean $AUC_{0–24h}$ was below the study target of 80% of the value seen in adults (63.1 mg·h/L vs. 71.8 mg·h/L), but the trough values that were observed at 23.1 hours to 25.1 hours after the previous dose exceeded the trough plasma concentration recommended for treatment-experienced adults (0.55 mg/L).[14] One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to DRV; the $AUC_{0–24}$ was 47.8 mg·h/L.

Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Background Therapy in Children, Adolescents, and Adults

Population	n	Dose of DRV/r	AUC_{12h} (mcg·h/mL) Median[a]	C_{0h} (ng/mL) Median[a]
Children Weighing 10 kg to <15 kg[a]	13	20 mg/kg/3 mg/kg	66.0	3,533
Children Weighing 10 kg to <15 kg[a]	4	25 mg/kg/3 mg/kg	116.0	8,522
Children Weighing 15 kg to <20 kg[a]	11	20 mg/kg/3 mg/kg	54.2	3,387
Children Weighing 15 kg to <20 kg[a]	14	25 mg/kg/3 mg/kg	68.6	4,365
Children Aged 6 Years to <12 Years[b]	24	Determined by weight bands[b]	56.4	3,354
Adolescents Aged 12 Years to <18 Years[b]	50	Determined by weight bands[b]	66.4	4,059
Adults Aged >18 Years (Three studies)	285/278/119	600 mg/100 mg	54.7–61.7	3,197–3,539

[a] Source: U.S. Food and Drug Administration. FDA clinical pharmacologic review of darunavir. 2011. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf.

[b] DRV/r was administered at doses of 375 mg/50 mg twice daily for patients weighing 20 kg to <30 kg, 450 mg/60 mg twice daily for patients weighing 30 kg to <40 kg, and 600 mg/100 mg twice daily for patients weighing ≥40 kg. Data from the 2008 FDA pharmacokinetics review. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf.

[c] Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017lbledt.pdf.

Key: AUC_{12h} = 12-hour area under the curve; C_{0h} = pre-dose concentration; DRV/r = darunavir/ritonavir

Dosing

Pharmacokinetic Enhancers

DRV should not be used without a PK enhancer (boosting agent). RTV may be used as a boosting agent in children and adults. COBI may be used as a boosting agent in children weighing ≥40 kg and adults.

A study that enrolled 19 Thai children used the RTV 100-mg capsule twice daily as the boosting dose for twice-daily DRV 375 mg (in children weighing 20 kg to <30 kg), 450 mg (in children weighing 30 kg to 40 kg), and 600 mg (in children weighing ≥40 kg).[15] The DRV exposures with RTV 100 mg twice daily were similar to those obtained in the studies with lower (<100 mg) doses of liquid RTV.[12,15] The tolerability and PK data from this small study support the use of RTV 100 mg for boosting using either the powder or tablet formulation in children weighing ≥20 kg, particularly in instances where the lower-dose formulations are unavailable or a child does not tolerate the liquid RTV formulation. No data are available on the safety and tolerability of using the RTV 100-mg tablet or powder formulation in children weighing <20 kg.

Data on the dosing of DRV/c are available primarily for adult patients.[16] Data on once-daily use of the FDC tablet DRV/c 800 mg/150 mg (Prezcobix) showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.[14]

In an open-label switch study, eight adolescent patients with a median age of 14 years (range 12–17 years) who received DRV/c had DRV exposures (AUC_{tau}) that were similar to those observed in adults, except for a lower trough concentration at the end of the dosing interval (C_{tau}). The median DRV C_{tau} (494 ng/mL) was above the protein binding-adjusted half-maximal inhibitory concentration for wild-type virus (55 ng/mL). Adolescent patients in this study received the adult dose of COBI 150 mg daily. DRV dosing was based on weight, with patients who weighed ≥40 kg receiving DRV 800 mg once daily and patients who weighed 30 kg to <40 kg receiving DRV 675 mg once daily. In this small sample, 95.5% of patients had HIV RNA <50 copies/mL at Week 12. COBI appeared to be well tolerated with no discontinuations due to adverse events.[17]

Frequency of Administration

In February 2013, the FDA approved the use of once-daily DRV for treatment-naive children and for treatment-experienced children without DRV resistance-associated mutations (see Table B below). Population PK modeling and simulation were used to develop recommendations for once-daily dosing in younger pediatric subjects aged 3 years to <12 years and weighing 10 kg to <40 kg.[7,18] Currently, limited data exist on the efficacy of once-daily DRV/r dosing in treatment-naive or treatment-experienced children aged <6 years. Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years (see Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg below). The Panel recommends that once-daily DRV/r be used only in treatment-naive and treatment-experienced adolescents weighing ≥40 kg who do not have mutations that are associated with DRV resistance. If DRV and RTV are used once daily in children aged <12 years, the Panel recommends conducting a PK evaluation of plasma concentrations of DRV and closely monitoring viral load.

Table B. Food and Drug Administration–Approved Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg Who Are Treatment Naive or Treatment Experienced with No Darunavir Resistance-Associated Mutations

Note: The Panel generally recommends dosing DRV plus RTV twice daily in children aged ≥3 years to <12 years.

Weight	Dose (Once Daily with Food)
10 kg to <11 kg[a]	DRV 350 mg (3.6 mL)[b] plus RTV 64 mg (0.8 mL)[c]
11 kg to <12 kg[a]	DRV 385 mg (4 mL)[b] plus RTV 64 mg (0.8 mL)[c]
12 kg to <13 kg[a]	DRV 420 mg (4.2 mL)[b] plus RTV 80 mg (1 mL)[c]
13 kg to <14 kg[a]	DRV 455 mg (4.6 mL)[b] plus RTV 80 mg (1 mL)[c]
14 kg to <15 kg[a]	DRV 490 mg (5 mL)[b] plus RTV 80 mg (1 mL)[c]
15 kg to <30 kg	DRV 600 mg (tablet, combination of tablets, or 6 mL) plus RTV 100 mg (tablet, powder, or 1.25 mL)[c]
30 kg to <40 kg	DRV 675 mg (combination of tablets or 6.8 mL)[b,d] plus RTV 100 mg (tablet or 1.25 mL)[c]
≥40 kg	DRV 800 mg (tablet, combination of tablets, or 8 mL)[d] plus RTV 100 mg (tablet or 1.25 mL)[c]

[a] The dose in children weighing 10 kg to 15 kg is DRV 35 mg/kg and RTV 7 mg/kg per dose, which is higher than the weight-adjusted dose in children with higher weights.

[b] DRV 100 mg/mL oral suspension; the 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.

[c] RTV 80 mg/mL oral solution.

[d] The 6.8-mL and 8-mL DRV doses can be taken as two administrations (3.4 mL and 4 mL, respectively) once daily by refilling the oral dosing syringe supplied by the manufacturer or as one administration once daily if a larger syringe is provided by a pharmacy or provider.

Key: DRV = darunavir; RTV = ritonavir

Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg

During the TMC114-C228 trial, the researchers investigated once-daily dosing of DRV for 2 weeks; DRV PKs were evaluated in treatment-experienced children aged 3 years to <12 years as part of a substudy. After the conclusion of the substudy, the participants switched back to a twice-daily regimen.[18,19] The DRV/r dose for once-daily use, which was based on PK simulation and which did not include a relative bioavailability factor, was DRV 40 mg/kg coadministered with approximately 7 mg/kg of RTV for children weighing <15 kg and DRV/r 600 mg/100 mg once daily for children weighing ≥15 kg.[18,19] The PK data obtained from 10 children aged 3 to 6 years in this substudy (see Table C below) were included as part of the population PK modeling and simulation that was used to determine the FDA-approved dose for once-daily DRV/r in children aged 3 years to <12 years.

In a small study in which DRV/r was administered once daily to 12 treatment-experienced children aged 6 to 12 years,[9] the geometric mean AUC_{0-24h} achieved was below the study target of 80% of the value seen in adults (63.1 mg·h/L vs. 71.8 mg·h/L). Trough values exceeded the plasma concentration that is recommended for treatment-experienced patients (0.55 mg/L). Despite the FDA dosing guidelines, the Panel generally recommends dosing DRV/r twice daily in children aged

≥3 years to <12 years. The Panel makes this recommendation because of the small data set used for once-daily DRV/r PK modeling and the limited amount of data on the use of once-daily DRV/r in children aged <12 years.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Background Therapy

PK Parameter	Children Aged 3 to 6 Years (n = 10)[19]	Adults (n = 335)
DRV AUC_{24h} geometric mean, ng·h/mL (SD)	115 (40.6)	89.7 (27.0)
DRV C_{0h} geometric mean, ng/mL (SD)	3,029 (1,715)	2,027 (1,168)

Key: AUC_{24h} = 24-hour area under the curve; C_{0h} = pre-dose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

Once-Daily Administration in Adolescents Aged ≥12 Years and Weighing ≥40 kg

A substudy of once-daily dosing of DRV/r 800 mg/100 mg demonstrated that DRV exposures in 12 treatment-naive adolescents (aged 12–17 years and weighing ≥40 kg) were similar to those seen in adults treated with once-daily DRV (see Table D below).[20] After 48 weeks, 83.3% of patients had viral loads <50 copies/mL and 91.7% had viral loads <400 copies/mL.[10] Interestingly, no relationship was observed between DRV AUC_{24h} and C_{0h} and virologic outcome (HIV RNA <50 copies/mL) in this study. DRV exposures were found to be similar to those observed in adults with once-daily dosing in another study in which a single dose of DRV 800 mg with RTV 100 mg was administered to 24 subjects with a median age of 19.5 years (range 14–23 years).[21] However, DRV exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting that higher doses may be needed in younger adolescents. A single case report involving a highly treatment-experienced adolescent patient suggests that using an increased DRV dose with standard RTV boosting and employing TDM can lead to virologic suppression.

Table D. Darunavir Pharmacokinetics with Once-Daily Administration in Adolescents Aged ≥12 Years and Adults Aged >18 Years

Population	n	Dose of DRV/r	AUC_{24h}[a] (mcg·h/L) Median	C_{0h} (ng/mL) Median
Adolescents Aged 12–17 Years (Mean age 14.6 years)[20]	12	800 mg/100 mg	86.7	2,141
Adolescents and Adults Aged 14–23 Years (Mean age 19.5 years)[21]	24	800 mg/100 mg	69.5	1,300
Adults Aged >18 Years (Two studies)[a]	335/280	800 mg/100 mg	87.8–87.9	1,896–2,041

[a] Source: Darunavir [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021976Orig1s063lbl.pdf.

Key: AUC_{24h} = 24-hour area under the curve; C_{0h} = pre-dose concentration; DRV/r = darunavir/ritonavir

The efficacy of once-daily DRV has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.[10,22]

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Lopinavir/Ritonavir (LPV/r, Kaletra)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

<table>
<tr><th colspan="2">Formulations</th></tr>
<tr><td colspan="2">

Oral Solution

- [Kaletra] Lopinavir 80 mg/mL and ritonavir 20 mg/mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

Film-Coated Tablets

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

</td></tr>
<tr><th>Dosing Recommendations</th><th>Selected Adverse Events</th></tr>
<tr><td rowspan="3">

Neonate (Aged <14 Days) Dose

- Lopinavir/ritonavir (LPV/r) is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

Dosing for Individuals Who Are Not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

Infant (Aged 14 Days–12 Months) Dose

- Once-daily dosing **is not recommended.**
- LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both per kg body weight) twice daily. Use of this dose in infants aged <12 months is associated with lower LPV trough levels than those found in adults; LPV dosing should be adjusted for growth at frequent intervals (see Pharmacokinetics and Dosing below).

Child and Adolescent (Aged >12 Months to 18 Years) Dose

- Once-daily dosing **is not recommended.**
- LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily (maximum dose LPV/r 400 mg/100 mg twice daily, except as noted below). For patients weighing <15 kg, this dose approximates LPV/r 13 mg/3.25 mg (both per kg body weight)

</td><td>

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, alteration of taste
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- PR interval prolongation
- QT interval prolongation and Torsades de Pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below)

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<tr><th>Special Instructions</th></tr>
<tr><td>

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. **Do not crush or split tablets.**
- LPV/r oral solution should be administered with food, because a high-fat meal increases absorption.

</td></tr>
</table>

twice daily. For patients weighing ≥15 kg to 45 kg, this dose approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is the preferred dose for antiretroviral therapy (ART)-experienced patients who could harbor virus with decreased LPV susceptibility (see Pharmacokinetics and Dosing).

- LPV/r 230 mg/57.5 mg per m^2 of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients weighing <15 kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing ≥15 kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose **should not be used** in treatment-experienced patients who could harbor virus with decreased LPV susceptibility.

Weight-Band Dosing for Lopinavir 100-mg/Ritonavir 25-mg Pediatric Tablets in Children and Adolescents

Recommended Number of LPV/r 100-mg/25-mg Tablets Given Twice Daily		
Dosing target	300 mg/m^2 per dose given twice daily	230 mg/m^2 per dose given twice daily
Body Weight		
15 kg to 20 kg	2	2
>20 kg to 25 kg	3	2
>25 kg to 30 kg	3	3
>30 kg to 35 kg	4[a]	3
>35 kg to 45 kg	4[a]	4[a]
>45 kg	4[a] or 5[b]	4[a]

[a] Two tablets that each contain LPV/r 200 mg/50 mg can be substituted for the four LPV/r 100-mg/25-mg tablets in children who are capable of swallowing a larger tablet.

[b] In patients who weigh >45 kg and who are receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV), the FDA-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

Adult (Aged >18 Years) Dose

- LPV/r 800 mg/200 mg once daily; *or*
- LPV/r 400 mg/100 mg twice daily
- **Do not use** once-daily dosing in children; adolescents; in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV; or in patients with three or more LPV-associated mutations (see Special Instructions for a list of mutations).

- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Formulations below).
- LPV/r oral solution can be kept at room temperature (up to 77ºF or 25ºC) if used within 2 months. If kept refrigerated (36ºF to 46ºF or 2ºC to 8ºC), LPV/r oral solution remains stable until the expiration date printed on the label.
- Children aged <18 years who receive once-daily dosing of LPV/r have shown considerable variability in plasma concentrations and have a higher incidence of diarrhea. Therefore, once-daily dosing **is not recommended** for this age group.
- Use of LPV/r once daily is **contraindicated** if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher LPV trough concentrations may be required to suppress resistant virus.

Metabolism/Elimination

- Cytochrome P450 3A4 substrate and inhibitor.

Lopinavir/Ritonavir Dosing in Patients with Hepatic Impairment

- LPV/r is primarily metabolized by the liver. Use caution when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

Dosing for Individuals with Three or More Lopinavir-Associated Mutations (See Special Instructions for List) • LPV/r 400 mg/100 mg twice daily **Dosing for Individuals Receiving Concomitant Nevirapine or Efavirenz** • These drugs induce LPV metabolism and reduce LPV plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs. Once-daily dosing **should not be used** in these patients. *Child and Adolescent (Aged >12 Months to 18 Years) Dose* • LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily. See the table above for weight-band dosing when using tablets. *Adult (Aged >18 Years) Dose* • The FDA-approved dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing. Once-daily dosing **should not be used.** **Lopinavir/Ritonavir Used in Combination with Maraviroc** • Maraviroc doses may need modification (see the Maraviroc section).	

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Lopinavir/ritonavir (LPV/r) is a cytochrome P450 (CYP) 3A4 substrate and inhibitor with the potential for multiple drug interactions. Coadministering LPV/r with drugs that induce CYP3A4 may decrease LPV plasma concentrations, whereas coadministering LPV/r with other CYP3A4 inhibitors may increase LPV plasma concentrations. Coadministering LPV/r with other CYP3A4 substrates may require dose adjustments and additional monitoring.
- Before initiating therapy with LPV/r, a patient's medication profile should be carefully reviewed for potential drug interactions. In patients treated with LPV/r, fluticasone (a commonly used inhaled and intranasal steroid) should be avoided, and an alternative steroid should be used. Drug interactions with antituberculous drugs are common; patients who are receiving both LPV/r and antituberculous drugs may need a dose adjustment for LPV/r, or they may need to switch to an antiretroviral (ARV) regimen that does not include LPV/r.

Major Toxicities

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance.[1] Hyperlipidemia, especially hypercholesterolemia and hypertriglyceridemia,[2-4] which may be more pronounced in girls than in boys.[5] LPV requires a higher dose of ritonavir (RTV) than some other protease inhibitors (PIs); this higher dose may exacerbate these adverse events (AEs).

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, hepatitis (which has been life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and Torsades de Pointes may occur.
- *Special populations—neonates:* An increased risk of toxicity in premature infants has been reported, including cases of transient symptomatic adrenal insufficiency,[6,7] life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),[8-10] lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be caused by the drug itself and/or by the inactive ingredients in the oral solution,[10] which include propylene glycol (15.3%) and ethanol (42.4%). Transient asymptomatic elevation in 17-hydroxyprogesterone levels has also been reported[6] in term newborns treated at birth with LPV/r. The pharmacokinetics (PKs) and safety of LPV/r were studied in IMPAACT P1106, an opportunistic, multi-arm, Phase 4 prospective study in newborns who received ARV and anti-tuberculosis medicines in clinical care. A total of 25 neonates with HIV were enrolled, with a median birth weight of 2,130 g (interquartile range [IQR] 1,775–2,630 g) and a median gestational age of 35 weeks (IQR 32–37 weeks). Neonates received LPV/r solution at a dose of 300 mg/75 mg per m^2 twice daily, which was well tolerated and not associated with any treatment-related AEs, even in 13 newborns who initiated therapy prior to 42 weeks postmenstrual age at a mean postnatal age of 37 days (range 13–61 days).[11]

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

LPV/r is approved by the U.S. Food and Drug Administration (FDA) for use in children, including neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. The potential benefit of using LPV/r in premature infants who have not met these age thresholds must be carefully balanced with the risk of metabolic and cardiac toxicity. In pediatric patients receiving LPV/r at a dose of 300 mg/75 mg per m^2 twice daily, lower LPV exposure has been observed in infants aged <6 weeks relative to older children.[12]

Efficacy

Clinical trials involving antiretroviral therapy (ART)-naive adults have shown that regimens that contain LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens, including regimens that contain atazanavir, darunavir (DRV), fosamprenavir (FPV), saquinavir/ritonavir, or efavirenz (EFV). Studies also have shown that regimens that contain LPV/r plus two NRTIs are superior to regimens that contain nelfinavir (NFV) and inferior to regimens that contain DRV.[13-21]

LPV/r has been studied in both ART-naive and ART-experienced children and has demonstrated durable virologic activity and acceptable toxicity.[22-30]

Pharmacokinetics

General Considerations

Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m^2. For the adult dose of LPV/r 400 mg/100 mg, the scaled pediatric dose would be approximately LPV/r 230 mg/57.5 mg per m^2 of body surface area. However, younger children have enhanced LPV clearance and need higher doses to achieve LPV exposures that are similar to those seen in adults treated with standard doses. To achieve a trough concentration (C_{trough}) similar to that observed in adults, the pediatric dose needs to be increased 30% greater than the dose that is directly scaled for body surface area. LPV exposures in infants[12,24,29] are compared to those in older children[22] and adults[31] in Table A below.

Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age

PK Parameters	Adults (n = 19)[31]	Children (n = 12)[22]	Children (n = 15)[22]	Infants[a] at 12 Months (n = 20)[29]	Infants at 6 Weeks–6 Months (n = 18)[24]	Infants at 14 Days to <6 Weeks (n = 9)[12]
LPV Dose	400 mg	230 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2	300 mg/m^2
AUC_{0-12} (mcg·hr/mL)	92.6	72.6	116.0	101.0	74.5	43.4
C_{max} (mcg/mL)	9.8	8.2	12.5	12.1	9.4	5.2
C_{trough} (mcg/mL)	7.1	4.7	7.9	4.9	2.7	2.5
C_{min} (mcg/mL)	5.5	3.4	6.5	3.8	2.0	1.4

[a] This column contains unreported data that were originally generated for a published study. The data were provided by Edmund Capparelli, Pharm.D., in a personal communication (April 18, 2012).

Note: Values are means; all data come from studies wherein none of the participants received non-nucleoside reverse transcriptase inhibitors as part of their antiretroviral therapy.

Key: AUC = area under the curve; C_{max} = maximum concentration; C_{min} = minimum concentration; C_{trough} = trough concentration; LPV = lopinavir; mcg = microgram; mg = milligram; mL = milliliter; PK = pharmacokinetic

Models suggest that diet, body weight, and postnatal age are important factors in LPV PKs, with improved bioavailability as dietary fat increases during the first year of life[32] and with clearance slowing by age 2.3 years.[33] A study from the United Kingdom and Ireland compared outcomes of LPV/r treatment with either 230 mg per m^2 of body surface area per dose or 300 mg per m^2 of body surface area per dose in children aged 5.6 to 12.8 years at the time of LPV/r initiation. The findings suggested that the higher dose was associated with improved long-term viral load suppression.[34]

Pharmacokinetics and Dosing

14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

The PKs of the oral solution at approximately LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily were evaluated in infants aged <6 weeks[12] and infants aged 6 weeks to 6 months.[24] Even at this higher dose, C_{trough} levels were highly variable, but they were lower in infants than in children aged >6 months. C_{trough} levels were lower in infants aged ≤6 weeks than in infants aged 6 weeks to 6 months. By age 12 months, LPV area under the curve (AUC) was similar to that found in older children.[29] Because infants grow rapidly in the first months of life, it is important to optimize LPV dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg per m^2 of body surface area in older children and adolescents,[25] some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg per m^2 of body surface area dose to allow for projected growth between clinic appointments.

12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

Lower trough concentrations have been observed in children receiving LPV/r 230 mg/57.5 mg per m^2 of body surface area per dose twice daily than in children receiving LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily (see Table A above).[21] Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily (when LPV/r is given without nevirapine [NVP], EFV, FPV, or NFV), rather than the FDA-approved dose of LPV/r 230 mg/57.5 mg per m^2 of body surface area per dose twice daily.

For infants receiving LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily, immediate dose reduction at age 12 months **is not recommended;** many practitioners would allow patients to "grow into" the LPV/r 230 mg/57.5 mg per m^2 of body surface area per dose twice daily dose as they gain weight over time. Some practitioners would continue the infant dose (LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily) while using the LPV/r liquid formulation.

Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

In both children and adults, the LPV C_{trough} is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant FPV or NFV. Higher doses of LPV are recommended when the drug is given in combination with NVP, EFV, FPV, or NFV. In 14 children who were treated with LPV/r 230 mg/57.5 mg per m^2 of body surface area per dose twice daily plus NVP,[22] the mean LPV C_{trough} was 3.77 ± 3.57 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, but the variability in concentration is much higher in children than in adults.[22,35] In a study of 15 children with HIV aged 5.7 to 16.3 years who were treated with LPV/r 300 mg/75 mg per m^2 of body surface area per dose twice daily plus EFV 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in LPV trough concentrations. Five of 15 children (33%) had LPV 12-hour trough concentrations that were <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type

HIV.[36] A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/75 mg per m^2 of body surface area twice daily plus EFV 350 mg per m^2 of body surface area once daily reported only one patient (6.6%) with subtherapeutic LPV trough concentrations,[37] perhaps because the trial used an EFV dose that was approximately 11 mg/kg body weight[37] instead of the 14 mg/kg body weight dose used in the trial discussed above.[36]

Dosing

Once Daily

A single daily dose of LPV/r 800 mg/200 mg is approved by the FDA for treatment of HIV in treatment-naive adults aged >18 years. However, once-daily administration **cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM);** once-daily administration may be successful in select, closely monitored children.[38] There is high interindividual variability in drug exposure for LPV/r, and trough plasma concentrations may fall below the therapeutic range for wild-type virus, as demonstrated in studies of ARV-naive children and adolescents.[39-42] The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.[42,43] An international, randomized, open-label trial attempted to demonstrate that once-daily LPV/r dosing was noninferior to twice-daily LPV/r dosing in children and adolescents with HIV. This trial was unsuccessful, because a greater number of children and adolescents who received once-daily doses had viral loads ≥50 copies/mL within 48 weeks.[44]

Dosing and Its Relation to Efficacy

LPV/r is effective in treatment-experienced patients with severe immune suppression,[45,46] although heavily pre-treated patients may be slower to reach undetectable viral loads[46,47] and may have less-robust CD4 T lymphocyte (CD4) percentage responses.[48]

The relationship between LPV exposure and the susceptibility of the HIV-1 isolate is a key component of successful treatment. The ratio of C_{trough} to half maximal effective concentration (EC_{50}) is called the inhibitory quotient (IQ), and in both adults and children treated with LPV/r, viral load reduction is more closely associated with IQ than with either C_{trough} or EC_{50} alone.[49-51] One study investigated the use of the IQ as a guide for therapy by administering higher doses of LPV/r to children and adolescents until a target IQ of 15 was reached. This study showed that doses of LPV/r 400 mg/100 mg per m^2 of body surface area per dose twice daily (without FPV, NFV, NVP, or EFV) and LPV/r 480 mg/120 mg per m^2 of body surface area per dose twice daily (with NVP or EFV) were safe and tolerable.[25] Results of a modeling study suggest that standard doses of LPV/r may be inadequate for treatment-experienced children and suggest the potential utility of TDM when LPV/r is used in children who were previously treated with PIs.[52] An LPV plasma concentration of ≥1 mcg/mL is cited as a minimum target C_{trough},[53-55] but this trough concentration may not adequately control viremia in patients with multiple LPV resistance mutations.[56,57]

Formulations

Palatability

The poor palatability of the LPV/r oral solution can be a significant challenge to medication adherence for some children and families. Numbing the taste buds with ice chips before or after administering the solution, masking the taste of the solution by administering it with sweet or tangy foods (e.g., chocolate syrup, peanut butter), or having the pharmacist flavor the solution prior to dispensing it are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.[58,59]

Do Not Use Crushed Tablets

LPV/r tablets must be swallowed whole. Crushed tablets are slowly and erratically absorbed, and result in significantly reduced AUC, maximum concentration (C_{max}), and C_{trough} compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5–75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.[60] In a PK study that used a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate LPV C_{trough} measurements.[43]

Toxicity

Children treated with LPV/r may have less-robust weight gain and smaller increases in CD4 percentage than children treated with NNRTI-based regimens.[27,61-65] However, one study did not observe this difference in the effect of LPV/r on CD4 count,[66] and another study found that the difference did not persist after a year of therapy.[30] Some studies found no differences between the weight gain of children treated with LPV/r and those treated with EFV.[64,67] Switching to an EFV-based regimen at or after age 3 years removed the risk of LPV-associated metabolic toxicity, with no loss of virologic control (see Table 16 in Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy).[64,65] Bone mineral density improved when children were treated with EFV-containing regimens instead of regimens that contained LPV/r.[68] Among 212 children randomized to either remain on an LPV/r-based regimen or switch to an EFV-containing regimen, osteocalcin—a biochemical marker of bone turnover—was higher in the LPV/r group compared with the EFV group at both 8 weeks and 2 years post-randomization. Levels of C-telopeptide of type 1 collagen (CTx) and procollagen type I N-terminal propeptide did not differ between the two groups.[69]

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Entry and Fusion Inhibitors

Fostemsavir (FTR, Rukobia)

Ibalizumab (IBA, Trogarzo)

Maraviroc (MVC, Selzentry)

Fostemsavir (FTR, Rukobia)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Extended-release tablet: 600 mg

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Child and Adolescent (Aged <18 years) Dose

- The safety and efficacy of using fostemsavir (FTR) in children and adolescents aged <18 years have not been established.

Adult Dose

- One tablet twice daily

Selected Adverse Events

- QTc (corrected QT) prolongation with higher than recommended dosages
- Increased hepatic transaminases in patients with hepatitis B or hepatitis C coinfection

Special Instructions

- Can be taken with or without food.
- Extended-release tablet must be swallowed whole. Do not chew, crush, or split tablets.
- Should not be coadministered with strong cytochrome P450 (CYP) 3A4 inducers of metabolism, such as rifampin, carbamazepine, phenytoin, and phenobarbital.
- Potential for multiple drug interactions. Check concomitant medications before prescribing FTR.
- Tablets have slight odor similar to vinegar.

Metabolism/Elimination

- FTR tromethamine is a prodrug of temsavir (TMR), an HIV-1 gp120-directed attachment inhibitor.
- FTR is rapidly converted to TMR after oral administration. Metabolic pathways of TMR include hydrolysis (esterases) (36.1% of oral dose), oxidation (CYP3A4) (21.1% of oral dose), and uridine diphosphate glucotransferase (UDG) (<1% of oral dose).
- TMR is a substrate of CYP3A, esterases, P-glycoprotein, and breast cancer resistance protein (BCRP).
- TMR is an inhibitor of organic anion transporter (OAT) P1B1 and OATP1B3; TMR and two of its metabolites are inhibitors of BCRP.

Fostemsavir Dosing in Patients with Hepatic Impairment

- No dose adjustment is required in patients with mild-to-severe hepatic impairment.

Fostemsavir Dosing in Patients with Renal Impairment

- No dose adjustment is required in patients with renal impairment or those on hemodialysis.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

Metabolism: Coadministration with strong cytochrome P450 3A inducers is contraindicated, because the plasma concentrations of the active metabolite, temsavir (TMR), are significantly reduced, which could result in loss of virologic efficacy.

Cardiac toxicity: Caution is required when used in combination with drugs that are associated with prolongation of the QTc interval of the echocardiogram.

Oral contraceptives: Do not exceed 30 mcg ethinyl estradiol daily. The combination may increase ethinyl estradiol concentrations and risk of thrombosis.

HMG-CoA reductase inhibitors (statins): TMR may increase plasma concentrations of statins.

Other antiretroviral agents: Etravirine may decrease TMR plasma concentrations, but when it is used in combination with a ritonavir-boosted protease inhibitor (strong inhibitor), the overall effect on TMR metabolism is negligible and does not require dose modification.

Major Toxicities

More common: Nausea reported in ≥5% of patients.

Less common: QTc prolongation with higher than recommended doses.[1] Increased hepatic transaminases in patients with hepatitis B or hepatitis C coinfection.

Resistance

The International AIDS Society–USA maintains a list of HIV drug resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

TMR showed reduced antiviral activity against HIV subtype AE (the predominate subtype found in Southeast Asia but not commonly found elsewhere in the world). Treatment-emergent glycoprotein (gp120) genotypic substitutions at four key sites (S375, M434, M426, and M475) have been found in evaluable subjects with virologic failure in clinical trials. However, overall frequency of polymorphisms previously associated with the potential to reduce susceptibility to TMR is low and should not be a barrier to its usage in patients with multidrug resistance. [2]

Pediatric Use

Fostemsavir (FTR) is a HIV-1 gp120-directed attachment inhibitor that is not approved for use in pediatric patients. FTR was approved by the U.S. Food and Drug Administration in 2020 for use in adults in combination with other antiretroviral (ARV) drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV failing their current (ARV) regimen due to resistance, intolerance, or safety considerations.[3] A pharmacokinetic and safety study of FTR in children and adolescents ≥20 kg will soon be open to enrollment. (PENTA Foundation: NCT04648280)

Efficacy in Clinical Trials

The safety and efficacy of FTR in heavily treatment-experienced adults with HIV were evaluated in the BRIGHTE trial, a Phase 3, double-blind placebo-controlled trial. A total of 371 participants were enrolled into two cohorts (randomized and nonrandomized), depending on remaining treatment options. The randomized cohort included 272 participants, with at least one fully active drug in at least one but no more than two ARV classes that could be added to FTR. Participants received either FTR or a placebo twice daily for 8 days, in addition to their failing ARV regimen. On Day 8, participants treated with FTR had a significantly greater decrease in levels of HIV-RNA than those taking the placebo (0.79 versus 0.17 $\log_{10}$ copies, respectively).[4] After Day 8, all participants received FTR as part of an optimized regimen. In results reported through 48 weeks,[4] 54% of participants had an HIV viral load of <40 copies/mL. At Week 96, 60% of participants[3] had HIV viral loads of <40 copies/mL and a mean increase in CD4 T lymphocyte (CD4) cell counts of 205 cells/mm^3. In 51% (27 out of 53) of evaluable subjects with virologic failure, treatment-emergent gp120 genotypic substitutions were detected at four key sites (S375, M434, M426, and M475). In the randomized cohort, virologic response rates increased over time, between the 24-week and 96-week analyses. Response rates were associated with better susceptibility scores for new optimized treatment regimens.[5] Patients with the lowest CD4 counts at baseline were more likely to experience serious adverse events or death.[5]

An additional nonrandomized cohort of 99 patients who had no active drugs as treatment options but had FTR added to an optimized ARV regimen was studied. Of these, 38% achieved an HIV viral load of <40 copies/mL at 48 weeks.[4] For this cohort, at 96 weeks,[3] 37% of participants had HIV viral loads of <40 copies/mL, and the mean increase in CD4 counts was 119 cells/mm^3.

Improvements in patient-reported outcomes in health-related quality of life were observed among participants in both cohorts of the BRIGHTE trial at 48 weeks.[6]

Mechanism of Action

FTR tromethamine is a prodrug of TMR, an HIV-1 gp120-directed attachment inhibitor. FTR is rapidly converted to TMR after oral administration. TMR binds directly to the HIV-1 gp120 and prevents viral attachment and subsequent entry of virus into host T cells. FTR has a novel mechanism of action and no *in vitro* cross-resistance with other ARVs, and it can be used regardless of HIV-1 tropism.[2]

Pharmacokinetics

FTR is pre-systemically metabolized to the active moiety TMR by alkaline phosphatase in the luminal surface of the small intestine, and then TMR is rapidly absorbed. In healthy adults, the estimated $t_{1/2}$ is approximately 11 hours.[7]

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Ibalizumab (IBA, Trogarzo)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations	
Single-Dose Vial for Intravenous Administration: 200 mg/1.33 mL (150 mg/mL) in a single-dose vial. Each single-dose vial contains the following inactive ingredients: L-histidine, polysorbate 80, sodium chloride, and sucrose. For additional information, see Drugs@FDA or DailyMed.	
Dosing Recommendations	**Selected Adverse Events**
Child and Adolescent Dose • The safety and efficacy of using ibalizumab (IBA) in children and adolescents has not been established. **Adult Dose** • A single-loading dose infusion of IBA 2,000 mg administered intravenously (IV) over 30 minutes is followed by a maintenance dose of IBA 800 mg administered IV over 15 minutes every 2 weeks. • U.S. Food and Drug Administration approval of IBA is limited to heavily treatment-experienced adults with multidrug-resistant HIV infection who are experiencing treatment failure on their current regimen. • IBA is used in combination with other antiretroviral drugs.	• Diarrhea, dizziness, nausea, rash • Immune reconstitution inflammatory syndrome • In studies of cynomolgus macaque monkeys, IBA use during pregnancy was associated with reversible immunosuppression (CD4+ T and B cell lymphopenia) in offspring with IBA exposure *in utero*.[1] Whether this association exists for infants of women treated with IBA during pregnancy is unknown. • Potential for immunogenicity in the form of anti-IBA antibodies **Special Instructions** • The solution in the vial must be diluted in 0.9% sodium chloride injection and administered by IV infusion. • Using aseptic technique, withdraw 1.33 mL from each vial and transfer into a 250-mL bag of 0.9% sodium chloride for IV injection. Other IV diluents must not be used. • Once diluted, the solution should be administered immediately. If not used immediately, the solution can be stored at room temperature for up to 4 hours or refrigerated for up to 24 hours. Refrigerated solution should be allowed to stand at room temperature for at least 30 minutes but no more than 4 hours prior to administration. • Diluted solution is administered as an IV infusion, not as a bolus or IV push. **Metabolism/Elimination** • Monoclonal antibodies are metabolized to peptides and amino acids.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- Ibalizumab (IBA) is a humanized IgG4 monoclonal antibody that blocks HIV entry into CD4 T lymphocyte (CD4) cells. Based on IBA's mechanism of action and target-mediated drug disposition, drug–drug interactions are not expected. However, no drug interaction studies have been conducted.[1]

Major Toxicities

- *More common:* Rash, diarrhea, headache, nausea, dizziness, depression[1,2]
- *Less common (more severe):* Immune reconstitution inflammatory syndrome (IRIS), hypersensitivity reaction[1]

Resistance

HIV has shown reduced susceptibility to IBA, as defined by a decrease in maximum percent inhibition, when HIV loses N-linked glycosylation sites in the V5 loop of glycoprotein 120.[1-3]

Phenotypic and genotypic test results showed no evidence of cross-resistance between IBA and any U.S. Food and Drug Administration (FDA)–approved classes of antiretroviral (ARV) drugs.[4] IBA exhibits ARV activity against R5-tropic, X4-tropic, and dual-tropic HIV.[4]

Pediatric Use

Approval

IBA is not approved by the FDA for use in pediatric patients. IBA was approved by the FDA in 2018 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are experiencing treatment failure on their current regimen.[5] IBA has an orphan drug designation exempting the requirement for pediatric studies under the Pediatric Research Equity Act. The FDA requested that the company create a registry to collect prospective data in individuals exposed to IBA during pregnancy to monitor maternal and pregnancy outcomes, including adverse effects on the developing fetus, neonate, and infant. Healthcare providers are encouraged to report these adverse events to Theratechnologies by calling 1-833-23-THERA (1-833-23-4372).

Efficacy in Clinical Trials

Trial Tai Med Biologics (TMB-301) was conducted in 40 adults aged 23 to 65 years who had body weights ranging from 50 kg to 130 kg, had resistance to ARV drugs from three classes, had been treated for at least 6 months on stable ARV regimens, had viral loads >1,000 copies/mL, and had viral sensitivity to at least one ARV drug.[3,5] Participants continued their current ARV regimens and received a 2,000-mg loading dose of IBA on Day 7 of the study. One week after the loading dose, participants optimized their ARV regimens. Participants received IBA 800 mg on Day 21 and every 2 weeks thereafter. At Week 25, 43% of participants achieved suppressed viral loads[1,3] of <50 copies/mL. At Week 48 of an open-label extension study, 24 participants were taking IBA and their optimized ARV regimen. Sixteen of 27 participants (59%) had viral loads <50 copies/mL at 48 weeks.[6,7]

Mechanism of Action

IBA is a recombinant humanized monoclonal antibody that blocks HIV from infecting CD4 cells. It does this by binding to domain 2 of the CD4 receptor, which interferes with the post-attachment steps that allow HIV virus particles to enter host cells and prevent the viral transmission that occurs via cell–cell fusion.[1,7] IBA does not interfere with CD4-mediated immune functions because it binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor, away from Major Histocompatibility Complex II molecule binding sites.

Embryo-Fetal Toxicity

In an enhanced pre- and post-natal development study, pregnant cynomolgus monkeys were administered intravenous doses of IBA and significant changes in infant monkey immune cell levels were found (CD4+ T cell and B cell lymphocytopenia) that were attributed to *in utero* IBA exposure.[1] The lymphocyte changes correlated with infant monkey IBA serum concentrations and appeared to return to near normal levels when IBA concentrations were nearly undetectable. One treatment-group infant monkey died from a systemic viral infection with secondary superficial bacterial infection that was acquired during the postnatal period. Despite the low incidence of death (1 of 20 infant monkeys), the death may be related to IBA-induced immunosuppression.[1]

Based on these animal data, IBA may cause reversible immunosuppression (CD4+ T cell and B cell lymphocytopenia) in infants born to mothers treated with IBA during pregnancy. Immune phenotyping of the peripheral blood and expert consultation are recommended to provide guidance regarding monitoring and management of exposed infants based on the degree of immunosuppression observed. Furthermore, the safety of administering live or live-attenuated vaccines to infants with *in utero* IBA exposure and abnormal lymphocyte levels is unknown.

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Maraviroc (MVC, Selzentry)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Oral Solution: 20 mg/mL

Tablets: 25 mg, 75 mg, 150 mg, 300 mg

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

- Maraviroc (MVC) is approved by the U.S. Food and Drug Administration (FDA) for use, in combination with other antiretroviral agents, for the treatment of CCR5-tropic HIV-1 infection in infants born full term weighing ≥2 kg, children, adolescents, and adults.

Recommended Maraviroc Dose for Full-Term Infants and Treatment-Experienced Children and Adolescents Weighing ≥2 kg: Tablets or Oral Solution

Weight Band	Twice-Daily Dosing	Oral Solution 20 mg/mL	Tablets
Recommended doses when MVC is given with non-interacting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine (NVP), enfuvirtide (T-20), and raltegravir (RAL)			
2 kg to <4 kg	30 mg	1.5 mL	N/A
4 kg to <6 kg	40 mg	2 mL	N/A
6 kg to <10 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
10 kg to 14 kg	150 mg	7.5 mL	One 150-mg tablet
14 kg to <30 kg	200 mg	10 mL	One 150-mg tablet and two 25-mg tablets

Selected Adverse Events

- Nausea, vomiting
- Abdominal pain, diarrhea
- Cough
- Upper respiratory tract infections
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally seen in patients with severe renal insufficiency)
- Dizziness

Special Instructions

- MVC is recommended for use in patients who have only CCR5-tropic HIV-1. Before using MVC, conduct testing with an HIV tropism assay (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines) to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use MVC if CXCR4-tropic or mixed/dual-tropic HIV is present.
- MVC can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet
≥40 kg	300 mg	15 mL	One 300-mg tablet
Recommended doses when MVC is given with potent cytochrome P450 (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including all protease inhibitors (PIs)			
2 kg to <10 kg	**Not recommended.** Data are insufficient to make dosing recommendations for infants weighing <10 kg and receiving a potent P450 CYP3A inhibitor.		
10 kg to <20 kg	50 mg	2.5 mL	Two 25-mg tablets
20 kg to <30 kg	75–80 mg	4 mL	One 75-mg tablet
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
≥40 kg	150 mg	7.5 mL	One 150-mg tablet
Recommended doses when MVC is given with potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz (EFV) and etravirine (ETR)			
Infants and children and adolescents in all weight bands	**Not recommended.** Data are insufficient to make dosing recommendations.		

Recommended Maraviroc Dose for Adults: Tablets

When Coadministered With	Dose
Non-interacting concomitant medications, including NRTIs, T-20, NVP, and RAL	300 mg twice daily

Metabolism/Elimination

- MVC is a substrate of CYP3A4. If a patient is receiving antiretroviral agents or other medications that act as CYP3A inducers or inhibitors, the dose of MVC should be adjusted accordingly.

Maraviroc Dosing in Patients with Hepatic Impairment

- Use caution when administering MVC to patients with hepatic impairment; MVC concentrations may be increased in these patients.

Maraviroc Dosing in Patients with Renal Impairment

- No data recommend specific doses of MVC for pediatric patients with mild or moderate renal impairment. MVC is **contraindicated** for pediatric patients with severe renal impairment or end-stage renal disease who are on regular hemodialysis and who are receiving potent CYP3A inhibitors.
- Refer to the manufacturer's prescribing information for the appropriate doses to use in adolescent and adult patients with renal impairment.

Potent CYP3A inhibitors (with or without a potent CYP3A inducer), including all PIs	150 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor), including EFV and ETR	600 mg twice daily

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Absorption:* Absorption of maraviroc (MVC) is slightly reduced with ingestion of a high-fat meal. Food restrictions were not part of either the adult trials (which used the tablet formulation) or the pediatric trial (which used both the tablet and oral solution formulations) that demonstrated the efficacy, antiviral activity, and safety of MVC. Therefore, MVC can be given with or without food.

- *Metabolism:* MVC is a cytochrome P450 (CYP) 3A and p-glycoprotein (P-gp) substrate and requires dose adjustments when administered with medications that modulate CYP3A or P-gp. A patient's medication profile should be carefully reviewed for potential drug interactions before MVC is administered; recommended MVC doses are based on concomitant medications and their anticipated effect on MVC metabolism.

Major Toxicities

- *More common:* Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, vomiting, diarrhea, and headache. Dizziness occurred in 12.2% of adults but only 3.2% of children when MVC was administered twice daily.

- *Less common (more severe):* Hepatotoxicity has been reported; some cases were preceded by evidence of a systemic allergic reaction (including pruritic rash, eosinophilia, or elevated levels of immunoglobulin). Serious adverse events (AEs) occurred in <2% of MVC-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

Mechanism of Action

MVC is a CCR5 receptor antagonist that selectively binds to the human chemokine receptor CCR5 on the cell membrane, preventing interaction between HIV-1 gp120 and CCR5 tropic HIV-1, inhibiting viral entry into the cell.

Resistance

An HIV tropism assay should be performed before MVC is administered to a patient. Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants. However, in circumstances when MVC is needed for presumptive HIV therapy for full-term neonates at high risk of perinatal HIV transmission, initiation of MVC should not be deferred until assay results are available, and consultation with an HIV expert is recommended.

Pediatric Use

Approval

MVC was recently approved by the U.S. Food and Drug Administration (FDA) for treatment in full-term infants weighing ≥2 kg when used in conjunction with other antiretroviral drugs.[1] MVC had previously been approved by the FDA for use in children ≥2 years and weighing ≥10 kg, as well as adolescents and adults who have CCR5-tropic HIV-1.[2]

Pharmacokinetics and Efficacy

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT 2007) study evaluated the pharmacokinetics (PK) and safety of MVC added to a 6-week prophylactic antiretroviral regimen to prevent perinatal HIV transmission of HIV among infants born to mothers living with HIV.[2] Analyses were stratified by exposure to efavirenz (EFV), either *in utero* or through breastmilk versus non-EFV exposure. The MVC exposure target was average plasma concentration (C_{avg}) ≥75 ng/mL, as determined by adult treatment studies. MVC oral solution was dosed at 8 mg/kg twice daily for the first 6 weeks of life. Among 25 infants with evaluable PK data, 12 of whom were EFV-exposed, 67% of the EFV-exposed infants achieved a C_{avg} ≥75 ng/mL at Week 1, whereas 77% of the EFV-unexposed infants had a C_{avg} ≥75 ng/mL. At Week 4, the proportion of infants achieving a C_{avg} ≥75 ng/mL declined to 42% among EFV-exposed infants and 31% among EFV-unexposed infants. No infants in the study met safety endpoints or discontinued MVC during the study and no infants acquired HIV. The FDA recommendation for MVC dosing among children >6 weeks of life but younger than 2 years of age is based on modeling using PK data from the IMPAACT 2007 study. When considering the use of MVC for neonates and infants, a pediatric HIV specialist should be consulted.

PK, safety, and efficacy of MVC for treatment-experienced children, ages 2 years to <18 years and weighing ≥10 kg, who had plasma HIV RNA >1,000 copies/mL, were examined in an international dose-finding and efficacy study (A4001031). Of the 103 children who participated in the study, 51% had HIV-1 subtype C, 25% had subtype B, and 23% had other subtypes.

In this trial, the MVC dose was based on body surface area and the composition of the patient's optimized background therapy. Most participants, [90 of 103 participants (87%)], received MVC in combination with potent CYP3A inhibitors; 10 participants received MVC with noninteracting medications; and only 3 participants received MVC with CYP3A inducers (without CYP3A inhibitors). The key pharmacologic target (geometric mean C_{avg} of >100 ng/mL) was achieved with both the tablet and oral solution formulation of MVC.[3]

From a mean baseline plasma HIV RNA concentration of 4.4 $\log_{10}$ copies/mL, a decrease of ≥1.5 $\log_{10}$ occurred in all four age-based cohorts. Only two participants discontinued the study due to AEs. The most common MVC-related AEs through 48 weeks were diarrhea (which occurred in 20.3% of participants), vomiting (19.8%), and upper respiratory infections (16.2%). At Week 48, 48% of participants had HIV RNA <48 copies/mL.[3] The absolute CD4 T lymphocyte cell count and percentage increased in all four subgroups of the study, with overall median increases of 192 cells/mm^3 (interquartile range [IQR] 92–352 cells/mm^3) and 4% (IQR 1% to 8%), respectively.

References

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Integrase Inhibitors

Bictegravir (BIC)

Cabotegravir (CAB, Vocabria)

Dolutegravir (DTG, Tivicay)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

Bictegravir (BIC)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Bictegravir is available only in a fixed-dose combination (FDC) tablet.

FDC Tablet

- [Biktarvy]
  - Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
  - Bictegravir 30 mg/emtricitabine 120 mg/tenofovir alafenamide 15 mg

When using FDC tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF)

Neonate or Child Aged <2 years and Weighing <14 kg

- No data currently are available on the appropriate dose of Biktarvy in children aged <2 years and weighing <14 kg. Studies are being conducted to identify the appropriate dose for this age and weight group.

Child (Aged ≥2 years), Adolescent, and Adult Dose

- One tablet once daily with or without food.

Body Weight	Dose
≥14 to <25 kg	BIC 30 mg/FTC 120 mg/TAF 15 mg
≥25 kg	BIC 50 mg/FTC 200 mg/TAF 25 mg

- The U.S. Food and Drug Administration approved Biktarvy for use in only antiretroviral therapy–naive patients or to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen and who have no history of treatment failure and no known mutations associated with resistance to the individual components of Biktarvy. Some members on the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation (see Efficacy in Clinical Trials in Adults below).

Selected Adverse Events

- Diarrhea, nausea, headache

Special Instructions

- Administer Biktarvy with or without food. See the Drug Interactions section below for guidance when administering Biktarvy with antacids or iron or calcium supplements.
- For children unable to swallow a whole tablet, the tablet can be split and each part taken separately as long as all parts are swallowed within approximately 10 minutes.
- Screen patients for hepatitis B virus (HBV) infection before using FTC or TAF. Severe acute exacerbation of HBV can occur when discontinuing FTC or TAF; therefore, monitor hepatic function for several months after halting therapy with FTC or TAF.

Metabolism/Elimination

- BIC is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase (UGT1A1).

	Biktarvy Dosing in Patients with Hepatic Impairment • Biktarvy **is not recommended** for use in patients with severe hepatic impairment. **Biktarvy Dosing in Patients with Renal Impairment** • Biktarvy **is not recommended** for use in patients with estimated creatinine clearance <30 mL/min. See the product label for use in patients on dialysis.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Bictegravir (BIC) is a substrate of cytochrome P450 (CYP) 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1. TAF is a substrate of P-glycoprotein and UGT1A1. Coadministration of the fixed-dose combination (FDC) tablet bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF [Biktarvy]) and rifampin is **contraindicated.**[1,2]
- *Renal effects:* BIC is an inhibitor of organic cation transporter 2 and multidrug and toxin extrusion protein 1, so it decreases tubular secretion of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate (eGFR) with no change in glomerular function. Drugs that decrease renal function could reduce clearance of FTC.
- *Absorption:* Administering BIC concurrently with antacids lowers the plasma concentrations of BIC. This occurs because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Chelation by high concentrations of divalent cations—such as iron—decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and BIC. For this reason, Biktarvy should be administered at least 2 hours before or 6 hours after antacids and supplements or multivitamins that contain iron, calcium, aluminum, magnesium, and/or zinc[3] when Biktarvy is given on an empty stomach. Biktarvy and antacids or supplements that contain calcium or iron can be taken together with food.

Major Toxicities

- *More common:* Diarrhea, nausea, headache. In two clinical trials, total bilirubin increased by up to 2.5 times the upper limit of normal in 12% of patients who received Biktarvy. In general, however, bilirubin increase was quite mild and did not lead to drug discontinuations in these trials.[2] BIC may cause an increase in creatine kinase concentration. One patient out of 201 in a post-marketing observational study in adults experienced thrombocytopenia,[4] and one participant out of 100 in a prospective cohort study in children and adolescents experienced insomnia/anxiety[5] leading to drug discontinuation. Weight gain has been reported in adults who were receiving Biktarvy (see Table 15h. Lypodystrophies and Weight Gain).
- *Less common (more severe):* Severe immune reconstitution inflammatory syndrome may be more common with INSTIs than with other antiretroviral (ARV) agents.

Resistance

The International Antiviral Society–USA maintains a list of HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

BIC, available as part of the FDC tablet Biktarvy, containing BIC 50 mg/FTC 200 mg/TAF 25 mg, was approved by the U.S. Food and Drug Administration (FDA) in 2018 for use in adults and in 2019 for use in children or adolescents weighing ≥25 kg. Biktarvy, containing BIC 30 mg/FTC 120 mg/TAF 15 mg was approved by the FDA in 2021 for use in children aged ≥2 years and weighing ≥14 to <25kg. Biktarvy is FDA approved for patients who have no ARV treatment history or to replace current ARV regimens in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 3 months, with no history of treatment failure and no known mutations associated with resistance to the individual components of the FDC.[2] However, some Panel members recommend the use of Biktarvy in patients with prior treatment failure and who have virus containing the M184V mutation (see Efficacy in Clinical Trials in Adults below).

Efficacy in Clinical Trials in Adults

In a short-term Phase 1 study, BIC monotherapy at doses of BIC 50 mg or BIC 100 mg was well tolerated. Three out of eight participants in both of these dosing groups achieved HIV RNA <50 copies/mL within 11 days.[6] The efficacy (defined as viral load suppression to HIV RNA <50 copies/mL) and safety (as measured by the incidence of study drug discontinuation or death) of Biktarvy were similar to the efficacy and safety of comparator regimens in two Phase 3 randomized trials in treatment-naive adults. Viral load suppression occurred in 89% of participants who received coformulated BIC 50 mg/FTC 200 mg/TAF 25 mg (n = 320) and in 93% of participants who received a regimen of dolutegravir (DTG) 50 mg plus FTC 200 mg plus TAF 25 mg (n = 325). Study drug discontinuation occurred in 1% of participants in both groups.

In a separate trial, viral load suppression occurred in 92% of participants who received BIC/FTC/TAF (n = 314) and in 93% of participants who received coformulated abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) (n = 315). Study drug discontinuation was not reported for any of the participants who received BIC/FTC/TAF, although it did occur in 1% of participants who received ABC/DTG/3TC.[2,7] Studies that randomized virologically suppressed patients who were on stable ARV regimens to either continue their current regimens or switch to coformulated BIC/FTC/TAF have shown that BIC/FTC/TAF has similar safety and efficacy to existing regimens. Viral load suppression occurred in 94% of participants who were randomized to switch to BIC/FTC/TAF (n = 282) and in 95% of participants who continued taking ABC/DTG/3TC (n = 281). Study drug discontinuation was reported in 2% of participants who received BIC/FTC/TAF and 1% of participants who received ABC/DTG/3TC. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (n = 290) achieved viral load suppression, whereas 89% of participants who continued receiving atazanavir-based or darunavir-based combination ARV regimens (n = 287) achieved viral load suppression. Study drug discontinuation occurred in 1% of participants in both groups.[2]

Initial studies in participants switching to BIC/FTC/TAF from stable antiretroviral therapy (ART) required undetectable viral load for 3 or 6 months and no proven or presumed preexisting resistance to any of the components of BIC/FTC/TAF.[2,8,9] Further analysis of data from these studies used proviral genotyping and showed presence of M184V/I mutation in 54 (10%) of 543 BIC/FTC/TAF-treated participants. Presence of this mutation did not affect viral load suppression, with Week 48 HIV RNA <50 copies/mL in 52 (96%) of 54 participants with archived M184V/I mutations compared with Week 48 HIV RNA <50 copies/mL in 561 (98%) of 570 participants without the mutation.[10] A study to measure the effect of preexisting nucleoside reverse transcriptase inhibitor (NRTI) mutations on virologic outcome in participants switching from a stable regimen to BIC/FTC/TAF showed Week 48 HIV RNA <50 copies/mL in 223 (94%) of 237 participants without M184V/I resistance and in 42 (89%) of 47 participants with M184V/I mutations at baseline.[11,12] At Week 48, HIV RNA <50 copies/mL was maintained in 199 (93%) of 213 participants with no NRTI resistance mutation and in 66 (93%) of 71 participants with any NRTI resistance mutation, including K65R/E/N, any number of thymidine analogue mutations (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N), T69 insertions, T69D, K70E/G/M/Q/S/T, L74I/V, V75A/S/M/T, Y115F, Q151M, or M184V/I.[11] That study required preenrollment virologic suppression for 6 months in those with suspected NRTI resistance and 3 months for those without suspected NRTI resistance.[11] In practice, Panel members have used BIC/FTC/TAF even in patients with detectable viral load, prior ARV failure, or preexisting NRTI mutations; this is based on the premise that the ability to simplify multi-pill or multi-dose regimens to a single small pill, once daily, can overcome potential resistance barriers with definite adherence benefits.[13]

Pharmacokinetics

Pharmacokinetic (PK) studies of Biktarvy containing BIC 50 mg, have been performed in adults, adolescents aged 12 years to <18 years who weigh ≥35 kg, and children aged 6 years to <12 years who weigh ≥25 kg. PK studies of "low-dose" Biktarvy, which contains BIC 30 mg, have been performed in children aged ≥2 years weighing 14 to <25 kg.[14] These studies show a higher BIC maximum serum concentration (C_{max}) in the younger cohorts than in the older cohorts, perhaps because the administered dose is higher on a mg/kg basis (see Table A below). The lower trough serum concentration (C_{tau}) and higher C_{max} in the younger age/lower body weight cohorts suggest more rapid clearance in children and adolescents than in adults. In the cohorts with body weight[14] ≥14 to <25 kg and body weight[5] ≥35 kg, there is a lower geometric mean ratio when C_{tau} is compared to adult values, and the lower 90% confidence interval suggests that some patients have quite rapid clearance (see Table B below). These PK observations raise the concern that some of the patients in the youngest age/lowest body weight cohorts may experience suboptimal trough concentrations, which may lead to less "pharmacologic forgiveness" in persons with lower adherence (see Table B below).[15]

Table A. Bictegravir Pharmacokinetics in Children, Adolescents, and Adults with HIV

PK Parameters	**Children** Aged ≥2 Years and Weighing ≥14 to <25 kg[14]	**Children** Aged 6 Years to <12 Years and Weighing ≥25 kg[5]	**Adolescents** Aged 12 Years to <18 Years and Weighing ≥35 kg[5]	**Adults**[2]
Dose (mg)	30	50	50	50
Dose for Lowest Weight in the Cohort (mg/kg)	2.14	2	1.43	1.25[a]
AUC_{tau} ng•h/mL Mean (CV%)	109,000 (24)	128,000 (28)	89,100 (31)	102,000 (26.9)
C_{max} ng/mL Mean (CV%)	10,100 (21)	9,460 (24)	6,240 (27)	6,150 (22.9)
C_{tau} ng/mL Mean (CV%)	2,000 (78)	2,360 (39)	1780 (44)	2,610 (35)

[a] This dose was calculated using 40 kg as the lowest weight for adults.

Key: AUC_{tau} = area under the concentration time curve over the dosing interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; CV = coefficient of variation; PK = pharmacokinetic

Table B. Bictegravir Pharmacokinetics in Children and Adolescents with HIV

Cohort Characteristics	Dose (mg)	Dose for Lowest Weight in Cohort (mg/kg)	GMR% (90% CI) Compared to Adult Values[a]		
			AUC_{tau}	C_{max}	C_{tau}
Aged ≥2 Years and Weighing ≥14 to <25 kg[14]	30	2.14	109 (96.7, 122)	166 (149, 184)	67.7 (49.6, 92.4)
Aged 6 Years to <12 Years and Weighing ≥25 kg[5]	50	2	125 (117–134)	153 (143–163)	88.9 (80.6-98.0)
Aged 12 Years to <18 Years and Weighing ≥35 kg[5]	50	1.43	86 (80–93)	100 (94–107)	65.4 (58.3–73.3)

[a] In this table, child and adolescent pharmacokinetic (PK) values are compared to the PK values of adults who received bictegravir 50 mg. The dose for the lowest weight in the adult cohort was 1.25 mg/kg; this was calculated using 40 kg as the lowest weight for adults.

Key: AUC_{tau} = area under the concentration time curve over the dosing interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; CI = confidence interval; GMR = geometric mean ratio

Use of Biktarvy in Children and Adolescents Weighing ≥25 kg

BIC 50 mg/FTC 200 mg/TAF 25 mg (Biktarvy) was administered to adolescents aged 12 years to <18 years who weighed ≥35 kg (maximum body weight 56.1 kg) and who had had viral loads of <50 copies/mL for ≥6 months on their previous ARV regimens. The drug was well tolerated, and was associated with a fall in eGFR similar to that seen in adults. This decrease in eGFR was considered to be from changes in tubular secretion of creatinine and was not a true change in glomerular function. In comparing cohorts of children (body weight ≥14 kg to <25 kg) and adolescents (body weight ≥35 kg) to adult cohorts the geometric mean ratio of C_{tau} was noted to be lower (see Tables A and B above). All 50 participants in the study had viral loads <50 copies/mL at Week 24, and 49 of 50 had viral loads <50 copies/mL at week 48.[5]

BIC 50 mg/FTC 200 mg/TAF 25 mg was administered to children aged 6 years to <12 years who weighed ≥25 kg and who had had viral loads <50 copies/mL for ≥6 months on their current ARV regimens.[5] Despite a high AUC and C_{max} (see Table A above), the drug combination was well tolerated, with a fall in eGFR similar to that seen in adult studies. One participant stopped the study drug because of insomnia and anxiety. The geometric mean ratio of C_{tau} compared with adult values (see Table B above) showed trough concentrations similar to those seen in adults.[5] All 50 participants in the study had viral loads <50 copies/mL at Week 24 and 49 of 50 had viral loads <50 copies/mL at Week 48.[5]

Use of Biktarvy in Children Weighing ≥14 to <25 kg

Biktarvy tablets consisting of BIC 30 mg/FTC 120 mg/TAF15 mg were administered to children aged ≥2 years weighing ≥14 to <25 kg and who had viral load <50 copies/mL on stable ART. PK evaluation showed high AUC and C_{max}, similar to those in patients aged 6 years to <12 years who weighed ≥25 kg, a similarly low C_{tau} (see Table A above), and a lower geometric mean ratio when C_{tau} was compared with adult values (see Table B above).[14] In general, the low-dose tablet was well tolerated over 55 weeks in the 22 children studied.[16] Adverse events considered related to the study drug included transient neutropenia (n = 2) and abdominal pain (n = 3).[16] At 24 weeks, the median change in CD4 cell count was −100 cells/µL, and the change in CD4 percentage was +0.5%. HIV RNA at <50 copies/mL was maintained in 20 of 22 participants at 24 weeks.[16]

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Cabotegravir

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Cabotegravir (CAB, Vocabria)
Cabotegravir for Intramuscular Injection (CAB, Apretude)
Cabotegravir and Rilpivirine for Intramuscular Injections (IM CAB and RPV, Cabenuva)

Formulations
Tablets • Cabotegravir: 30 mg **Single-Dose Vial for Intramuscular Injection** • [Apretude] Cabotegravir 600-mg/3-mL (200-mg/mL) suspension for intramuscular injection for use as HIV pre-exposure prophylaxis only **Co-Packaged Formulation** • [Cabenuva Kit] Cabotegravir 600-mg/3-mL (200-mg/mL) and rilpivirine 900-mg/3-mL (300-mg/mL) suspension for intramuscular injection (each drug packaged in a separate syringe) • [Cabenuva Kit] Cabotegravir 400-mg/2-mL (200-mg/mL) and rilpivirine 600-mg/2-mL (300-mg/mL) suspension for intramuscular injection (each drug packaged in a separate syringe) When using the co-packaged formulation, refer to the Rilpivirine section for additional information. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
[Apretude] Cabotegravir for Intramuscular Injection • Cabotegravir (CAB) 600 mg/3 mL for intramuscular (IM) injection is approved by the U.S. Food and Drug Administration (FDA) for use as HIV pre-exposure prophylaxis (PrEP) in adults and adolescents weighing ≥35 kg after an oral dosing lead-in period of approximately 1 month. See package insert for additional information about dosing and administration of CAB as PrEP; this indication is not addressed in the Pediatric Antiretroviral Guidelines. **[Cabenuva] Cabotegravir and Rilpivirine (IM CAB and RPV)** *Pediatric Dose* • CAB tablets and co-packaged cabotegravir and rilpivirine intramuscular injections (IM CAB and RPV) are not FDA approved for the treatment of HIV in children aged <12 years.	• Depression • Insomnia • Headache • Rash (can be severe and include drug reaction with eosinophilia and systemic symptoms) or hypersensitivity • Hepatotoxicity • Altered adrenocorticotropic hormone stimulation test of uncertain clinical significance • Injection site reactions • Creatine phosphokinase elevation following IM injection • Weight gain

Child and Adolescent (Aged ≥12 Years and Weighing ≥35 kg) and *Adult Dose*	Special Instructions
• CAB and RPV is a two-drug co-packaged product for IM injection that is FDA approved as a complete regimen for the treatment of HIV-1 in patients with HIV RNA levels <50 copies/mL on a stable antiretroviral (ARV) regimen, with no history of treatment failure, and no known or suspected resistance to CAB or RPV. • Oral lead-in dosing with CAB and RPV for at least 28 days can be used to assess tolerability prior to initiating IM CAB and RPV injections or patients can proceed directly to IM CAB and RPV on the last day of their current ARV regimen. • Refer to the package insert for instructions about changing the frequency of IM injections, i.e., from monthly to every-2 month dosing or from every-2-month to monthly dosing. **Oral Lead-In Dosing** ○ CAB 30 mg orally and RPV 25 mg orally once daily with a meal for at least 28 days. **Dosing for Monthly Administration of IM CAB and RPV** ○ On the last day of oral lead-in therapy or the current oral ARV regimen, a loading dose of CAB 600 mg (3 mL) and RPV 900 mg (3 mL) should be given as two separate IM injections in separate ventrogluteal sites. ○ Continuation therapy of CAB 400 mg (2 mL) and RPV 600 mg (2 mL) IM is given 1 month after the loading dose and once a month thereafter, with allowance for a ±7-day administration window. **Dosing for Every-2-Month Administration of IM CAB and RPV** ○ To initiate every-2-month dosing, CAB 600 mg (3 mL) and RPV 900 mg (3 mL) should be given as two separate IM injections in separate ventrogluteal sites on the last day of oral lead-in or the current oral ARV regimen and 1 month after the initial injections. ○ After these two initiation injections 1 month apart for 2 months, continuation therapy with IM CAB 600 mg (3 mL) and RPV 900 mg (3 mL) is administered every 2 months, with allowance for a ±7-day administration window. Patients should be monitored for approximately 10 minutes for post-injection reactions. A 23-gauge, 1.5-inch IM needle is recommended for the injection and is provided in the packaging. Longer, 2-inch needles (not included with packaging) should be used in patients with a body mass index >30 kg/m^2. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends that providers review instructions available with the package insert prior to beginning IM administration of CAB and RPV. In-person training also may be helpful and can be requested from the manufacturer (ViiV).	• Coadministering oral RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV. Refer to the RPV package insert for specific instructions regarding use of these products during the oral lead-in dosing. • If monthly injections are missed or delayed by more than 7 days and oral therapy has not been taken, clinically reassess the patient to determine if resumption of injection dosing remains appropriate. Refer to the package insert for information about managing planned and unplanned missed doses. • IM CAB and RPV is a complete regimen. Coadministration with other ARV drugs is not recommended. • When IM CAB and RPV injections are stopped, residual concentrations may remain measurable for up to 12 months or longer. It is essential to initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injections of IM CAB and RPV. • Use CAB and RPV with caution when coadministering it with a drug that has a known risk of prolonging the QTc interval or causing Torsades de Pointes (for more information, see CredibleMeds). **Metabolism/Elimination** • CAB is metabolized by uridine diphosphate-glucuronosyl transferase (UGT)1A1. • RPV is a cytochrome P450 3A substrate. **Dosing in Patients with Hepatic Impairment** • No dose adjustment of CAB or IM CAB and RPV is necessary in patients with mild or moderate hepatic impairment. **Dosing in Patients with Renal Impairment** • RPV decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration. • No dose adjustment of CAB or IM CAB and RPV is necessary in patients with mild or moderate renal impairment. However, IM CAB and RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Cabotegravir (CAB) is metabolized primarily by uridine diphosphate-glucuronosyl transferase (UGT)1A1. Drugs that are strong inducers of UGT1A1 may decrease CAB concentrations and decrease effectiveness.
- Rilpivirine (RPV) is a cytochrome P450 (CYP) 3A substrate, and RPV concentrations may be affected when administered with CYP3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before CAB plus RPV is administered.
- CAB and RPV are both highly protein bound and unlikely to be removed by hemodialysis.
- Coadministering oral RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
    - Antacids should not be taken less than 2 hours before or less than 4 hours after oral RPV.
    - H2 receptor antagonists should not be administered less than 12 hours before or less than 4 hours after oral RPV.
    - Do not use oral RPV with proton pump inhibitors.
- Rifamycin drugs significantly reduce CAB and RPV plasma concentrations. For patients who are concomitantly receiving rifabutin and RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal. Coadministration of the following drugs **is contraindicated:**
    - Rifampin and RPV
    - Rifampin or rifapentine and CAB
    - Rifabutin and intramuscular (IM) CAB and RPV

Major Toxicities

- *More common:* Injection site reactions, insomnia, headache, rash, elevated creatine phosphokinase serum concentrations
- *More common:* In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotropic hormone stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, 6 out of 30 patients (20%) developed this abnormality.[1] The clinical significance of these results is unknown.
- *Less common (more severe):* Depression or mood changes, suicidal ideation
- *Rare:* Hepatotoxicity, post-injection reactions including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure
- *Rare:* RPV drug-induced liver injury has been reported.[2]

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

CAB oral tablets (Vocabria) and co-packaged CAB and RPV for injection (Cabenuva) were recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of HIV in children or adolescents aged ≥12 years and weighing ≥ 35 kg and adults. They are not approved for use in children aged<12 years. CAB tablets were approved by the FDA in 2021 for use in adults as part of the oral lead-in prior to beginning injectable IM CAB and RPV or as an oral interim treatment when patients will miss planned injections.[1,3] CAB and RPV co-packaged extended-release injectable suspensions for IM use are approved for use in patients (monthly or every 2 months) who are virologically suppressed on a stable antiretroviral (ARV) regimen with no history of virologic failure or known resistance affecting either of the component drugs.[1]

In December 2021, the FDA approved CAB IM (Apretude) for HIV pre-exposure prophylaxis (PrEP) in adults and adolescents weighing at least 35 kg; injections are started after an oral lead-in period of approximately 1 month. Refer to the package insert for additional information about dosing and administration,[4] and see the Centers for Disease Control and Prevention Guidelines for Pre-Exposure Prophylaxis for the Prevention of HIV in the United States for further information about the use of CAB for PrEP.

Efficacy in Clinical Trials

The safety and efficacy of CAB, an HIV-1 integrase inhibitor, given in combination with RPV, a non-nucleoside reverse transcriptase inhibitor (NNRTI), have been evaluated in a series of clinical trials conducted in adults. To date, all studies have included a 4-week oral lead-in period to assess for toxicity prior to initiating the IM CAB and RPV regimen.

The Phase 3 Antiretroviral Therapy as Long-Acting Suppression (ATLAS) study randomized stable, virologically suppressed adults to receive either CAB and RPV (n = 308) or continue their oral antiretroviral therapy (ART) (n = 308). Patients assigned to CAB and RPV initiated therapy with an oral regimen for 4 weeks prior to beginning monthly IM injections. The initial assessment at 48 weeks demonstrated that switching to monthly IM CAB and RPV was noninferior to continuing a three-drug oral therapy. After 48 weeks, participants were allowed to transition to injections every 2 months in a follow-up study (ATLAS-2M, see below); 52 patients remaining on the original ATLAS study were included in the 96-week analysis. One-hundred percent of patients continuing monthly IM CAB and RPV maintained HIV-1 RNA <50 copies/mL compared to 97% of those switching to IM CAB and RPV from their initial oral ART. Adverse events were more common among patients receiving injectable ART; injection site reactions were common, but only 1% withdrew from the study because of these events.[5] The ATLAS-2M trial randomized participants to monthly IM CAB 400 mg and RPV 600 mg (n = 523) or every-2-month injections of CAB 600 mg and RPV 900 mg (n = 522); it enrolled both new patients and those continuing from the ATLAS trial. After 48 weeks, the every-2-month injections were noninferior to monthly injections, with eight confirmed virologic failures in the every 2-month injection group and two in the monthly injection group. Of those failing the every 2-month injection regimen, 5 of 8 had archived NNRTI resistance-associated mutations at baseline.[6]

The First Long-Acting Injectable Regimen (FLAIR) study enrolled 631 treatment-naive adults and initiated treatment with a standard oral ARV regimen consisting of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) for 20 weeks. Those patients with documented HIV-1 RNA <50 copies/mL after 16 weeks were randomized to either continue oral DTG/ABC/3TC (n = 283) or switch to oral CAB and RPV for 4 weeks, followed by monthly injections of CAB and RPV (n = 283). After 96 weeks of randomized therapy, nine participants in each arm had HIV RNA >50 copies/mL. Adverse events were common in both treatment groups, but adverse events leading to withdrawal from the study were observed in only 14 (5%) participants in the IM CAB and RPV group and 4 (1%) in the oral standard care group. Injection site reactions were the most common adverse events, reported by 245 (88%) participants in the IM CAB and RPV group, and lasted a median of 3 days.[7]

These studies demonstrated noninferiority of switching to monthly IM CAB and RPV compared to continuing oral ART. In all studies, adult patients expressed a high degree of treatment satisfaction and preference for the IM CAB and RPV regimen. International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Study 2017, More Options for Children and Adolescents (MOCHA), is currently in progress to evaluate the safety, tolerability, acceptability, and pharmacokinetics of this injectable regimen in adolescents (NCT03497676).

Pharmacokinetics

IM CAB reaches its maximum plasma concentration in adults in about 7 days and has a mean half-life of 5.6 to 11.5 weeks. Measurable levels of CAB can be detected in plasma for up to a year or longer. Due to this prolonged drug exposure, it is essential to initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injections of CAB and RPV to minimize the potential risk of developing viral resistance.[1]

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Dolutegravir (DTG, Tivicay, Tivicay PD)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Tablets

Dispersible tablets for oral suspension [Tivicay PD] 5 mg

Film-coated tablets [Tivicay] 10 mg, 25 mg, 50 mg

Fixed-Dose Combination Tablets

- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Neonate Dose

- Dolutegravir (DTG) is not approved by the U.S. Food and Drug Administration (FDA) for use in neonates.

[Tivicay PD] Dolutegravir Dispersible Tablets

Infant (Aged ≥4 Weeks and Weighing ≥3 kg), Child, and Adolescent Dose

- DTG dispersible tablets are approved by the FDA for use in pediatric patients who are treatment naive or treatment experienced but naive to integrase strand transfer inhibitor (INSTI) treatment.

Pediatric Body Weight	Recommended Dose[a] of Dolutegravir Dispersible Tablets	Number of 5-mg Tablets
3 kg to <6 kg	5 mg once daily	1
6 kg to <10 kg	15 mg once daily	3
10 kg to <14 kg	20 mg once daily	4

Selected Adverse Events

- Insomnia
- Headache
- Neuropsychiatric symptoms (i.e., depression and/or suicidal thoughts or actions), especially in patients with a history of psychiatric illness
- Rare cases of hypersensitivity reactions, including rash and drug reaction (or rash) with eosinophilia and systemic symptoms, constitutional symptoms, and organ dysfunction (including liver injury)

Special Instructions

- DTG may be taken without meals.
- DTG should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.
- Fully disperse the dispersible tablets in 5 mL of drinking water (if using one or three tablets) or in 10 mL of drinking water (if using four, five, or six tablets) in the supplied cup; swirl the suspension so that no lumps remain. After full dispersion and within 30 minutes of mixing, administer the oral suspension. Rinse the dosing cup with a small amount of water, and give this additional water to the child to

14 kg to <20 kg	25 mg once daily	5
≥20 kg	30 mg once daily	6

[a] If certain uridine disphosphate glucuronyl transferase (UGT) 1A or cytochrome P450 (CYP) 3A inducers are coadministered, administer DTG dispersible tablets twice daily (see the Drug Interactions section below).

[Tivicay] Dolutegravir Film-Coated Tablets

- For use in patients who are treatment naive or treatment experienced but naive to INSTI treatment

Child and Adolescent (Weighing ≥14 kg)

- **DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis. Each formulation has different doses.**

Dosing of Film-Coated Tablets for Pediatric Patients Weighing ≥14 kg Who Can Swallow Tablets

Pediatric Body Weight	Recommended Dose[a] of Dolutegravir Film-Coated Tablets	Number of Tablets
14 kg to <20 kg	40 mg once daily	4 × 10 mg
≥20 kg	50 mg once daily	1 50 mg

[a] If certain UGT1A or CYP3A inducers are coadministered, administer DTG tablets twice daily (see the Drug Interactions section below).

Some infants may have received raltegravir as presumptive HIV therapy prior to diagnosis. These infants and other infants and children with HIV who have received INSTIs are candidates to switch to once-daily DTG if they are virologically suppressed or have no mutations associated with resistance to INSTIs.

Adult Dose

- One 50-mg DTG film-coated tablet once daily
- If certain UGT1A or CYP3A inducers are coadministered, administer DTG 50 mg twice daily (see the Drug Interactions section below).
- Adults who are INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance should receive 50 mg DTG twice daily.

[Dovato] Dolutegravir/Lamivudine

Adult Dose

- One tablet once daily with or without food as a complete regimen in antiretroviral (ARV)-naive adults with no known

ensure the child takes the full dose and no medication remains in the dosing cup.

- DTG dispersible tablets may be swallowed whole. If more than one tablet is required, swallow one tablet at a time to reduce the risk of choking.
- No data exist regarding dispersion in breast milk or any vehicles other than water.
- In patients who have difficulty swallowing tablets whole, 50-mg tablets may be either split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately.**[1]
- The efficacy of DTG 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain lamivudine (3TC). Severe acute exacerbations of HBV can occur after discontinuation of 3TC. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection.

Metabolism/Elimination

- UGT1A1 and CYP3A substrate—Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes may increase DTG plasma concentrations.

Dolutegravir Dosing in Patients with Hepatic Impairment

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to the lack of data, DTG **is not recommended** for use in patients with severe hepatic impairment.
- FDC tablets containing ABC or 3TC should not be used in patients with impaired hepatic function.

Dolutegravir Dosing in Patients with Renal Impairment

- DTG decreases tubular secretion of creatinine and increases measured serum creatinine without affecting glomerular filtration.
- No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment, or in INSTI-experienced patients with mild or moderate renal impairment.
- Use DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.

mutations associated with resistance to the individual components of Dovato • Dovato is not approved by the FDA or recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) for use in children or adolescents as a complete regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug (see the Simplification of Treatment section below). **[Juluca] Dolutegravir/Rilpivirine** *Adult Dose* • One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months, with no history of treatment failure, and no known mutations associated with resistance to the individual components of Juluca • Juluca is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen (see the Simplification of Treatment section below). **[Triumeq] Abacavir/Dolutegravir/Lamivudine** *Child and Adolescent (Weighing ≥25 kg) and Adult Dose* • One tablet once daily with or without food • For use in patients who are ARV naive or ARV experienced (but INSTI naive) and who are not being treated with UGT1A1 or CYP3A inducers • See the Abacavir section for special instructions about testing for abacavir (ABC) hypersensitivity. • The FDA-approved dose for pediatric patients weighing ≥40 kg is one tablet once daily, but the Panel recommends use of this FDC for patients weighing ≥25 kg.	• FDC tablets containing 3TC or ABC should not be used in patients who have CrCl <50 mL/min or who are on dialysis.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker .

- *Metabolism:* Dolutegravir (DTG) is a uridine diphosphate glucuronyl transferase (UGT) 1A and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. DTG dosing should be adjusted to twice daily (i.e., twice the usual dose) for drugs such as efavirenz, rifampin, and some ritonavir-boosted protease inhibitors (PIs). Because etravirine (ETR) significantly reduces plasma concentrations of DTG, DTG **should not be administered** with ETR without coadministration of atazanavir (ATV)/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this effect on DTG concentrations. DTG **should not be administered** with nevirapine because of insufficient data on interactions between these drugs. See the product label for a full listing of significant drug–drug interactions.

- ATV is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients who were receiving DTG, patients who also received ATV had plasma concentrations of DTG that were twofold to fourfold higher than those of patients who received other antiretroviral (ARV) drugs.[2]
- Before administering DTG, clinicians should carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- *More common:* Insomnia and headache. Weight gain and increased body mass index (BMI) have been reported in adults who received DTG in clinical trials (see Table 15h. Lypodystrophies and Weight Gain) and in some pediatric and adolescent cohorts.[3-6]
- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional symptoms, and sometimes organ dysfunction; neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note that neuropsychiatric adverse effects (AEs) have occurred after initiation of DTG-based therapy in adults.[7,8]
- *Immune reconstitution inflammatory syndrome (IRIS):* In retrospective observational studies, severe cases of IRIS that required hospitalization appeared to be more frequent in patients who presented with advanced HIV disease and who initiated treatment with integrase strand transfer inhibitors (INSTIs), particularly DTG.[9,10] This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving INSTI-based therapy.
- *Rare:* Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of DTG. One of these cases required liver transplantation.[11,12]
- *Rare:* A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.[13]
- *Rare:* Early data from a prospective surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana showed a very small significant increase in the prevalence of neural tube defects (NTDs) among infants born to women who were receiving DTG at the time of conception that has declined over time.[14,15] In the most recent analysis of data through March 2021, the prevalence of NTDs among infants born to women on DTG at conception did not differ significantly from those born to women receiving non-DTG regimens.[16] Although the U.S. Food and Drug Administration (FDA) cautions that DTG should not be used during the first trimester of pregnancy because of potential teratogenicity, after a review of updated evidence regarding teratogenicity risks, the Perinatal Guidelines do not restrict use of DTG in female adolescents and adults who are pregnant or who may become pregnant. (See Appendix C. Antiretroviral Counseling Guide for Health Care Providers, Teratogenicity, and Recommendations for Use of Antiretroviral Drugs During Pregnancy and interventions to Reduce Perinatal HIV Transmission in the United States in the Perinatal Guidelines).

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

The efficacy of DTG 50 mg twice daily is reduced in patients with the INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

Pediatric Use

Approval

DTG is approved by the FDA for use, in combination with other ARV drugs, in pediatric patients at least 4 weeks of age AND weighing at least 3 kg who are treatment naive or treatment experienced but INSTI naive (see Appendix A, Table 2). Pediatric patients weighing ≥20 kg may take the DTG 50-mg film-coated tablets if they are able to swallow tablets. The combination tablet abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; Triumeq) is approved by the FDA for use in children and adolescents weighing ≥40 kg, although the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using it in children and adolescents weighing ≥25 kg (see Appendix A, Table 2). The combination tablets dolutegravir/rilpivirine (DTG/RPV; Juluca) and dolutegravir/lamivudine (DTG/3TC; Dovato) are not approved by the FDA for use in children or adolescents at the time of this review, and the Panel **does not recommend** using these drugs.

Formulation Differences: Film-Coated Tablet Compared to Dispersible Tablet

DTG is currently available as either film-coated tablets or dispersible tablets (tablets for oral suspension). The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,[17] so recommended doses using the dispersible tablet cannot be directly compared to those using the film-coated tablets. The drug exposure provided by the 50-mg film-coated tablet is approximately equal to that of DTG 30 mg administered as dispersible tablets.

Efficacy and Pharmacokinetics

Clinical Trials in Pediatric Patients 4 Weeks to <18 years

IMPAACT P1093 is an ongoing, multinational, open-label trial of DTG in children with HIV. Results of pharmacokinetic (PK), safety, and efficacy assessments have been reported sequentially for different age and weight cohorts as data became available; similarly, dosing recommendations have been revised sequentially.[18-20] Dosing recommendations that previously included the 25-mg film-coated tablets have been replaced with other formulations.

Data from IMPAACT P1093 Cohort 1 (aged 12 years to <18 years) and Cohort 2 (6 years to <12 years) provide support for use of DTG film-coated tablets in pediatric patients weighing ≥14 kg; Cohort 3 (2 to <6 years), Cohort 4 (6 months to <2 years), and Cohort 5 (4 weeks to <6 months) provide evidence supporting the use of DTG 5-mg dispersible tablets. Seventy-five study participants ranging in age from 1 month to 214 months received the currently approved dose (determined by weight and age) of DTG film-coated tablets or dispersible tablets. Eighty percent of participants were treatment-experienced, but all were INSTI naive. Among these 75 patients who received either DTG film-coated tablets or DTG dispersible tablets, according to the approved dosing recommendations for their weight band, 42 received DTG for at least 48 weeks. At Week 48, 69% of participants achieved HIV RNA <50 copies/mL, and 79% achieved HIV RNA <400 copies/mL. The median CD4 T lymphocyte count (percent) increase from baseline to Week 48 was 141 cells/mm^3 (7%). Overall, the safety profile in P1093 participants was comparable to that observed in adults, and both formulations were well tolerated by pediatric patients. The effectiveness observed in the trial was comparable to that of treatment-experienced adult subjects.[21]

Sixteen adolescents in Cohort 1 have remained on P1093 through 144 weeks, with 43% and 35% of participants achieving and maintaining HIV RNA levels <400 copies/mL and <50 copies/mL, respectively. Genotypic testing was available at the time of treatment failure for 6 of the 13 participants experiencing treatment failure; one of these adolescents developed DTG resistance.[22]

The Once-daily DTG based ART in Young people vS Standard thErapY (ODYSSEY) trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA), enrolled both treatment-naive and treatment-experienced pediatric patients from the European Union, Thailand, and several African countries; this trial initially evaluated doses approved by the European Medicines Agency at the time the trial started. A total of 707 children aged <18 years were enrolled; 311 children started DTG as first-line therapy, and 396 started DTG as second-line therapy.[23] Nested PK substudies within ODYSSEY also evaluated simplified pediatric dosing that aligned with the World Health Organization's recommended weight bands. PK data are available from a cohort of children weighing >25 kg who switched to the DTG 50-mg film-coated tablet. Data from another ODYSSEY cohort reported on children weighing 20 kg to <25 kg who received either the DTG 50-mg film-coated tablet or DTG 30 mg administered as six 5-mg dispersible tablets. Both of these doses achieved area-under-the-curve (AUC) and maximum plasma concentration (C_{max}) values that were higher than adult PK reference values but still acceptable. Both doses achieved trough plasma concentrations (C_{trough}) values that were slightly lower than adult reference values and exhibited greater variability but were determined to be acceptable.[24,25] Long-term safety and effectiveness assessments in the ODYSSEY trial are ongoing.

Combined PK data from P1093 and ODYSSEY across all age/weight cohorts form the basis for the current FDA dose recommendations and are summarized in Table A below. These data support the administration of either 30 mg as dispersible tablets or 50 mg as a film-coated tablet in patients weighing ≥20 kg. In addition, modeling and simulations that included UGT1A1 maturation in infants were used to support the dose of DTG in infants at least 4 weeks of age and weighing at least 3 kg. Dosing in neonates is under investigation.

Table A: Summary of Pharmacokinetic Parameters in Pediatric HIV-1-Infected Participants (Pooled Analyses for IMPAACT P1093 and ODYSSEY Trials)

Weight Band[a]	Dose[b] of DTG FCT or DTG DT	n	Pharmacokinetic Parameter Geometric Mean (%CV)		
			C_{max} (mcg/mL)	$AUC_{0\text{-}24h}$ (mcg·h/mL)	C_{24h} (ng/mL)
3 kg to <6 kg	DTG DT 5 mg once daily	8	3.80 (34)	49.37 (49)	962 (98)
6 kg to <10 kg	DTG DT 15 mg once daily	17	5.27 (50)	57.17 (76)	706 (177)
10 kg to <14 kg	DTG DT 20 mg once daily	13	5.99 (33)	68.75 (48)	977 (100)

14 kg to <20 kg	DTG DT 25 mg once daily	19	5.97 (42)	58.97 (44)	725 (75)
20 kg to <25 kg	DTG DT 30 mg once daily	9	7.16 (26)	71.53 (26)	759 (73)
≥20 kg	DTG FCT 50 mg once daily	49	4.92 (40)	54.98 (43)	778 (62)
Adults	DTG FCT 50 mg once daily	c	3.67 (20)	53.6 (27)	1,110 (46)
Adults	DTG FCT 50 mg once daily	c	4.15 (29)	75.1 (35)	2,120 (47)

[a] Data are from two weight-band-based pharmacokinetic substudies in the ODYSSEY trial.

[b]The bioavailability of DTG tablets for oral suspension is approximately 1.6-fold that of DTG film-coated tablets.

[c]Adult pharmacokinetic data are based on population pharmacokinetic analyses from clinical trials.[21]

Key: AUC_{0-24} = 24-hour area under the curve; C_{max} = maximum plasma concentration; C_{trough} = trough plasma concentration; CV = coefficient of variation, DTG DT = dolutegravir dispersible tablets; DTG FCT = dolutegravir film-coated tablets

Efficacy and safety of DTG-based regimens have been evaluated in multiple observational pediatric cohorts. Additional long-term efficacy and safety data for this age/weight group come from a retrospective, multicenter French cohort study that evaluated 50 adolescents who switched to DTG-based ART. Of 17 adolescents who were virologically suppressed at the time of DTG-based treatment, 14 (82%) maintained suppression, and 3 had transient viral rebound prior to re-achieving a plasma viral load <50 copies/mL. Of the 33 viremic adolescents who initiated DTG, 19 (58%) achieved sustained virologic success. Overall, 66% of patients achieved sustained virologic suppression, and 78% had undetectable plasma viral loads by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and were more likely to have had detectable viremia in the 6 months prior to DTG initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued DTG-based treatment because of a significant AE (dizziness and sleep disturbance).[26]

Another cohort of adolescents in Barcelona, Spain, received the fixed-dose combination (FDC) product ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Of the 12 patients described, one received Triumeq for initial ART, six received Triumeq for treatment simplification, and five received Triumeq because of previous treatment failure. Nine of the 12 patients achieved or maintained viral suppression after switching to Triumeq; three patients failed to achieve suppression because of suboptimal adherence. Of note, patients complained about the size of the tablet, and six patients reported having to crush or split the tablet to swallow it (see Appendix A, Table 2).[27]

The Baylor Tanzania Centres of Excellence program began rolling out DTG to children and adolescents in 2019 and recently reported on their experience.[28] Of the 1,703 children and adolescents initiating DTG between March 2019 and November 2020, 57% received tenofovir disoproxil fumarate (TDF)/3TC/DTG, 39% received ABC/DTG/3TC, and 4% received zidovudine/3TC/DTG. They reported no severe toxicity and no discontinuations of DTG. By the end of the study period, 92.4% of patients on DTG had documented viral suppression, including 85.6% (149 of 174 patients) of those not previously suppressed on their original regimen.

A dispersible tablet formulation of Triumeq (ABC 60 mg /DTG 5 mg/3TC 30 mg) is currently being studied in IMPAACT P2019 to confirm dosing of the three-drug FDC in pediatric patients younger than 12 years (NCT03760458). In P2019, children are dosed in five weight bands: ≥25 kg (one film-coated Truimeq tablet), 20 kg to <25 kg (six dispersible tablets), 14 kg to <20 kg (five dispersible tablets), 10 kg to <14 kg (four dispersible tablets), and 6 kg to <10 kg (three dispersible tablets). Results of the initial PK and safety assessments for 21 participants in weight bands ≥14 kg demonstrated acceptable PK parameters and tolerability for the three cohorts. No Grade 3 or 4 adverse events were reported, and no participant discontinued the study drug because of adverse events. The study is continuing to enroll the lower weight cohorts and will collect safety and efficacy data through 48 weeks.[29]

Pediatric Postmarketing Safety Studies

As long-term data are analyzed from the ODYSSEY trial, additional comparative safety information has been reported. The investigators reported a small number of neuropsychiatric AEs in the 707 children and adolescents randomized to DTG, not significantly different from those reported in study participants receiving standard care. However, participants receiving DTG were more likely to have suicidal ideation than those receiving standard care. Suicidal thoughts were reported by 13 participants receiving DTG, but none were reported among those receiving standard care; however, these symptoms were described as transient and did not lead to changes in ART.[30] In a subset of ODYSSEY participants aged 6 to <18 years, vitamin B12 and folate levels were measured to investigate a potential mechanism of reported neural tube defects among pregnant women receiving DTG. No differences were identified in vitamin B12 levels across study arms, although plasma and RBC folate levels were lower among participants receiving standard care.[31]

Reports of weight gain among adults enrolled in clinical trials prompted similar studies to investigate metabolic effects of DTG in adolescents. A group of investigators in Eswatini analyzed BMI measurements retrospectively from a cohort of 460 virally suppressed adolescents switching to a DTG-based regimen (either ABC/DTG/3TC or TDF/3TC/DTG). In this cohort, both weight-for-age z-score and BMI-for-age z-score decreased slightly before transition to DTG but increased during the year after DTG was initiated. The rate of BMI increase per year was calculated to be about twofold greater than the normal rate in the full cohort, and about 2.8-fold greater among female adolescents.[4] Another group measured multiple body fat parameters and cholesterol/lipid profiles in Italian adolescents switched from a PI- or non-nucleoside reverse transcriptase inhibitor-based regimen to a DTG-based regimen (ABC/DTG/3TC). Although BMI, body fat percentage, and limb fat percentage remained the same, trunk fat and trunk fat/total body fat ratio increased significantly. Total cholesterol and low density lipoproteins decreased, while serum triglycerides decreased early in the study and then increased by the end of the study.[3] A small, single-center cohort in Australia identified similar increases in BMI among adolescents switched to either DTG- or TAF-containing regimens.[5] Another retrospective analysis of a cohort of children and adolescents in the District of Columbia who were initiated on INSTIs also identified a pattern of increasing BMI-for-age z-scores, with a mean rate of change of +0.19 z-score units per year.[6] The ODYSSEY investigators also assessed weight, height, and BMI over the course of their prospective, randomized study. At Week 96, they found that weight, height, and BMI-for-age z-score increased in children receiving DTG compared with those receiving standard care, with the adjusted difference in means of 1 kg, 0.8 cm, and 0.14 z-score units, respectively. The investigators noted that the differences between treatment groups were relatively small, emerged early, and stabilized within the 2-year study period.[32]

Simplification of Treatment

Two trials in adults (Regimen Switch to Dolutegravir + Rilpivirine from Current Antiretroviral Regimen in Human Immunodeficiency Virus Type 1 Infected and Virologically Suppressed Adults, SWORD-1 and SWORD-2) supported the approval of a DTG 50-mg/RPV 25-mg FDC tablet as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 virologically suppressed patients who had been on stable ART for at least 6 months and who had no history of treatment failure or evidence of resistance mutations. The participants were randomized either to receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA levels <50 copies/mL.[33] After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV. At 148 weeks, 84% of the early-switch patients and 90% of the late-switch patients remained virologically suppressed, and only 11 patients receiving dual therapy met virologic failure criteria. No INSTI resistance was identified.[34] During the comparative randomized phase of the study, more AEs were reported and led to discontinuation in the DTG/RPV arm. In a subgroup of the SWORD study, small but statistically significant increases in hip and spine bone mineral density and bone turnover markers were observed in patients whose original ARV regimen contained TDF.[35] The approval of DTG 50 mg/3TC 300 mg as a complete regimen was supported by data from two randomized, double-blind, controlled trials (Efficacy, Safety, and Tolerability Study Comparing Dolutegravir Plus Lamivudine With Dolutegravir Plus Tenofovir/Emtricitabine in Treatment naïve HIV Infected Subjects, GEMINI-1 and GEMINI-2) in ARV-naive adults with HIV. GEMINI-1 and GEMINI-2 are identical 148-week trials that enrolled a total of 1,433 adults with HIV who had plasma HIV RNA levels between 1,000 copies/mL and ≤500,000 copies/mL at screening and no evidence of major resistance mutations or hepatitis B virus infection. Participants were randomized to receive either DTG plus 3TC or DTG plus 3TC/TDF. During 96 weeks of treatment, 86% of patients who received DTG plus 3TC and 89.5% of patients who received DTG plus 3TC/TDF achieved HIV RNA levels <50 copies/mL. Patients who received DTG plus 3TC had a lower rate of adverse drug reactions (19.6%) than those who received DTG plus 3TC/TDF (25%).[36]

Although neither Juluca nor Dovato is approved by the FDA for use in adolescents, the doses of the component drugs that make up these FDC tablets are approved for use in adolescents. The Panel usually endorses the use of adult formulations in adolescents, and these products may be appropriate for use in certain adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents who may have difficulty adhering to therapy, the Panel **does not currently recommend** using two-drug simplification regimens in adolescents and children until more data are available.

Crushing Film-Coated Tablets for Administration

Dispersible tablets are now considered the preferred formulation for pediatric patients weighing <20 kg, and film-coated tablets should not be used in children weighing <14 kg. In patients who have difficulty swallowing whole tablets and in children weighing >14 kg, when the preferred dispersible tablets are not available, the 10-mg and 50-mg tablets either may be split into halves followed by immediate ingestion of **both halves** of the tablet, or crushed and added to a small amount of semisolid food or liquid, all of which should be consumed **immediately.**[1] Crushing and mixing film-coated tablets would not be expected to adversely impact the product's pharmaceutical quality and, therefore, would not be expected to alter the intended clinical effect. This conclusion is based on the physicochemical and PK characteristics of the active ingredient and the *in vitro* dissolution behavior of the film-coated tablets in water. In healthy adults, the use of crushed tablets resulted in slightly higher exposures than the use of whole tablets.[37] No information exists on the impact of splitting or crushing film-coated tablets on palatability. Some case reports describe DTG-containing film-coated tablets' being crushed and successfully administered via orogastric tube[38] or nasogastric tube,[39] and it is expected that the dispersible tablets also may be administered similarly. If DTG is administered via enteral tube, care should be taken to disperse the tablets completely and flush the tube to avoid clogging.

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Elvitegravir (EVG)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Tablet: Discontinued by the manufacturer. Elvitegravir is available only in fixed-dose combination (FDC) tablets.

FDC Tablets

- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg

When using FDC tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (EVG/c/FTC/TAF)

Child (Weighing <14 kg) Dose

- No data exist on the dosing of EVG/c/FTC/TAF for children weighing <14 kg.

Child (Weighing ≥14 to <25 kg)

- Limited data currently exist on the appropriate dose of Genvoya in children ≥14 kg to <25 kg. Studies are being conducted to assess the safety and efficacy of a low-dose tablet with EVG 90 mg/COBI 90 mg/FTC 120 mg/TAF 6 mg.

Child and Adolescent (Weighing ≥25 kg) and Adult Dose

- One tablet once daily with food in antiretroviral therapy (ART)-naive patients. This dose of Genvoya also can be used to replace the current antiretroviral (ARV) regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/c/FTC/TDF)

Child and Adolescent (Weighing <35 kg) Dose

- No data exist on the appropriate dose of Stribild for children or adolescents weighing <35 kg.

Selected Adverse Events

Genvoya- and Stribild-Associated Adverse Events

- Nausea
- Diarrhea
- Fatigue
- Headache

Elvitegravir-Associated Adverse Events

- Diarrhea

Tenofovir Alafenamide–Specific Adverse Events

- Increased levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol

Tenofovir Disoproxil Fumarate–Specific Adverse Events

- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density
- Flatulence

Cobicistat-Specific Adverse Events

- Benign increases in serum creatinine levels (reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine

Special Instructions

Adolescent (Weighing ≥35 kg and Sexual Maturity Rating [SMR] 4 or 5) and Adult Dose • One tablet once daily with food in ART-naive patients. This dose of Stribild also can be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.	• Administer both Genvoya and Stribild with food. • Genvoya and Stribild should be administered at least 4 hours before or after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium. • When using Stribild, which contains TDF, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels >0.4 mg/dL should be closely monitored for renal safety. • Screen patients for hepatitis B virus (HBV) infection before using FTC, TDF, or TAF. Severe acute exacerbation of HBV can occur when FTC, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with FTC, TDF, or TAF. • For information on crushing and cutting tablets, see this table from Toronto General Hospital. **Metabolism/Elimination** • EVG is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9. • EVG is available only in combination with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the Cobicistat, TDF, and TAF sections for further details on these components. **Elvitegravir Dosing in Patients with Hepatic Impairment** • Stribild and Genvoya **should not be used** in patients with severe hepatic impairment. **Elvitegravir Dosing in Patients with Renal Impairment** • Stribild **should not be initiated** in patients with estimated CrCl <70 mL/min, and it should be discontinued in patients with estimated CrCl <50 mL/min. FTC and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet. • Genvoya is **not recommended** in patients with estimated CrCl <30 mL/min.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

Absorption: Elvitegravir (EVG) plasma concentrations are lower with concurrent administration of divalent cations due to the formation of complexes in the gastrointestinal tract and not due to changes in gastric pH. Therefore, Stribild and Genvoya should be administered at least 4 hours before or after administering antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.[1]

- *Metabolism:* Stribild and Genvoya contain EVG and cobicistat (COBI). EVG is metabolized predominantly by cytochrome P450 (CYP) 3A4, secondarily by uridine diphosphate glucuronyl transferase 1A1/3, and by oxidative metabolism pathways. EVG is a moderate inducer of CYP2C9. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. In addition, COBI inhibits the adenosine triphosphate-dependent transporters, P-glycoprotein and the breast cancer resistance protein, and the organic anion-transporting polypeptides OATP1B1 and OATP1B3. See the Cobicistat section for a more detailed summary of drug interactions. Multiple drug interactions are possible when using both EVG and COBI. Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain ritonavir (RTV), because of the similar effects of COBI and RTV on CYP3A4 metabolism. Coadministration of medications that induce or inhibit CYP3A4 may respectively decrease or increase exposures of EVG and COBI. Coadministration of medications that are CYP3A4 substrates may result in clinically significant adverse reactions that are severe, life-threatening, or fatal, or may result in loss of therapeutic effect if dependent on conversion to an active metabolite due to CYP3A4 inhibition by COBI.

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir, in the form of tenofovir disoproxil fumarate (TDF), or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Stribild. COBI inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL from baseline in adults. Creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, but the actual GFR might be only minimally changed.[2] Significant increases in serum creatinine levels >0.4 mg/dL from baseline may represent renal toxicity and should be evaluated. People who experience a confirmed increase in serum creatinine levels should be closely monitored for renal toxicity; clinicians should monitor creatinine levels for further increases and perform a urinalysis to look for evidence of proteinuria or glycosuria.[3]

Major Toxicities

More common: Nausea, diarrhea, fatigue, headache, flatulence

Less common (more severe): Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients receiving nucleoside reverse transcriptase inhibitors, including TDF and FTC. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children who were taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TDF, including a higher incidence of glycosuria, proteinuria, phosphaturia, and/or calciuria; increases in the levels of serum creatinine and blood urea nitrogen; and decreases in serum phosphate levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored if they are being treated with Stribild. This nephrotoxicity may be more pronounced in patients with preexisting renal disease.[3] Genvoya, which contains tenofovir alafenamide (TAF), has an improved bone and renal safety profile when compared to Stribild, which contains TDF, in children and adults.[4,5] However, Genvoya is associated with greater increases in lipid levels than Stribild, according to findings from large-scale clinical trials in adults.[6]

Resistance

The International Antiviral Society–USA maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation. There is phenotypic cross-resistance between EVG and raltegravir.[7]

Pediatric Use

Approval

Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [EVG/c/FTC/TAF]) is approved by the U.S. Food and Drug Administration (FDA) for use in antiretroviral (ARV)-naive children and adolescents with HIV weighing ≥25 kg with any sexual maturity rating (SMR). It also can be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.[6]

Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate [EVG/c/FTC/TDF]) is approved by the FDA as a complete regimen for use in children and adolescents aged ≥12 years and weighing ≥35 kg. However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting the use of Stribild to adolescents with SMRs of 4 or 5 due to concerns about decreased BMD in pre-pubertal patients. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.[3]

Efficacy in Clinical Trials in Adults

EVG/c/FTC/TDF was found to be noninferior to a regimen of efavirenz/emtricitabine/TDF (EFV/FTC/TDF)[8-10] and noninferior to a regimen of atazanavir/ritonavir (ATV/r) plus FTC/TDF in adults through 144 weeks of treatment.[11-13] In two studies, 1,733 adults were randomly assigned to receive either EVG/c/FTC/TDF or EVG/c/FTC/TAF.[5] After 48 weeks, those receiving EVG/c/FTC/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; $P < 0.0001$), significantly less proteinuria (median percent change in protein −3% vs. +20%; $P < 0.0001$), and a significantly smaller decrease in BMD at the spine (mean percent change −1.30% vs. −2.86%; $P < 0.0001$) and hip (−0.66% vs. −2.95%; $P < 0.0001$). Larger increases in fasting lipid levels were observed with EVG/c/FTC/TAF than with EVG/c/FTC/TDF; the median increases in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were all higher in patients who received EVG/c/FTC/TAF.

Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 Years and Weighing ≥35 kg

Studies of the use of Stribild and Genvoya in children with HIV aged ≥12 years and weighing ≥35 kg have demonstrated safety and efficacy similar to that seen in adults through 24 weeks and 48 weeks of study, respectively; these formulations are approved by the FDA for use in this age/weight group.[14,15] Stribild is not approved to treat children weighing <35 kg. Genvoya is preferred over Stribild when treating children with SMRs 1 to 3, because Genvoya carries a lower risk of renal and bone toxicity than Stribild. [6]Long-term bone safety data with Genvoya through 96 weeks revealed no concerns for toxicity in this age group[16] on the basis of BMD (median change from baseline spine BMD height-age [HA] z-score +0.14 and total body less head [TBLH] HA z-score of −0.07) and serum biomarkers of bone formation and resorption.[16]

Use of Elvitegravir as Genvoya in Children Weighing ≥25 kg

Genvoya is approved by the FDA to treat children with any SMR who weigh ≥25 kg; this approval was based on 24 weeks of data in 23 children.[17] In this study, children who had been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months were switched from their current regimens to Genvoya. No study discontinuations occurred due to medication toxicity, but a concerning decline in CD4 T lymphocyte (CD4) cell counts was observed in all 23 children over the first 24 weeks of Genvoya treatment. CD4 counts declined by a median of 130 cells/mm^3 (with a range of −472 cells/mm^3 to 266 cells/mm^3) from baseline. However, after enrolling additional children (for a total of 52 participants), the median CD4 count decline at 48 weeks[18] was 25 cells/mm^3 and at 96 weeks was 45 cells/mm^3. Additionally, the CD4 percentage did not significantly change[19] across Weeks 24, 48, and 96. The mechanism for the reduction in CD4 count is unclear, and this reduction has only been reported in this study. Plasma exposures of all four drugs were higher in these children than the plasma exposures seen in historical data from adults, but no association was identified between plasma exposures of the four components of Genvoya and CD4 counts.[20] Long-term bone safety data with Genvoya through 96 weeks revealed no concerns for toxicity in this cohort on the basis of BMD (median change from baseline spine BMD HA z-score −0.2 and TBLH HA z-score of −0.32) and serum biomarkers of bone formation and resorption.[19]

Use of Elvitegravir as Genvoya in Children Weighing 14 to <25 kg

EVG/c/FTC/TAF is not approved to treat children weighing <25 kg.[3,6] A pharmacokinetic (PK), safety, and efficacy study with a low-dose tablet in children aged ≥2 years and weighing ≥14 kg to <25 kg is ongoing.[21] In this study, children had to be virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months prior to entry. Virologic suppression was maintained[19] in 27 (100%) of 27 children at Week 16, 26 (96%) of 27 children at Week 24, and 26 (96%) of 27 children at Week 48. No participant discontinued the study drug because of adverse events or met criteria for resistance analyses through Week 48. CD4 counts decreased[19] by a mean of 187 cells/mm^3 between baseline and Week 48, although the CD4 percentage did not differ (mean [standard deviation (SD)] change of 0.0 [<5.0]). At least 90% of children reported that swallowing the low-dose tablet was "easy" or "super easy" and perceived the tablet size when swallowing as "okay" at baseline, Week 4, and Week 24.[21] Long-term bone safety data with the low-dose formulation through 48 weeks revealed no concerns for bone safety in this cohort[16] on the basis of BMD (median change from baseline in spine BMD HA z-score +0.14 and TBLH HA z-score of −0.06) and serum biomarkers of bone formation and resorption.

Pharmacokinetics

EVG/c/FTC/TDF (Stribild)

The PKs of EVG 150 mg, COBI 150 mg, FTC 200 mg, and TDF 300 mg as a fixed-dose combination (FDC) tablet were evaluated in 14 treatment-naive adolescents with HIV between 12 and <18 years of age and weighing ≥35 kg.[14] EVG area under the plasma concentration versus time curve over the dosing interval (AUC_{tau}) and peak concentrations (C_{max}) were 30% higher (90% confidence interval [CI], 105-162%) and 42% higher (90% CI, 116-173%), respectively, in comparison to historical data in adults. EVG concentrations at the end of the dosing interval (C_{tau}) were 6% higher (90% CI, 70-160%) than in adults, and approximately ninefold higher than the protein-adjusted 95% inhibitory concentration (PA-IC_{95}) of 44.5 ng/mL for EVG. COBI, FTC, and TFV exposures were comparable to those measured in adults.

Table A. Pharmacokinetics of EVG, COBI, FTC, and TFV from TDF (Stribild) in Adolescents with HIV Aged 12 to <18 Years and Weighing ≥35 kg

Component	Parameter	Adolescents Aged 12 to <18 Years and Weighing ≥35 kg[14]		Adults[a14]		% GLSM Ratio (90% CI)[14]
		n	GLSM	n	GLSM	
EVG	AUC_{tau} (ng·h/mL)	14	28,500	419	21,900	130 (105,162)
	C_{max} (ng/mL)	14	2,390	419	1,690	142 (116,173)
	C_{tau} (ng/mL)	14	410	419	387	106 (70,160)
COBI	AUC_{tau} (ng·h/mL)	14	9,200	483	8,729	105 (78,142)
	C_{max} (ng/mL)	14	1,275	483	1,179	108 (84,139)
	C_{tau} (ng/mL)	14	19	483	18	107 (66,173)
FTC	AUC_{tau} (ng·h/mL)	14	14,509	61	12,106	120 (103,139)
	C_{max} (ng/mL)	14	2,124	61	1,814	117 (101,136)
	C_{tau} (ng/mL)	14	98	61	104	94 (79,113)
TFV	AUC_{tau} (ng·h/mL)	14	4,281	419	3,114	137 (121,156)
	C_{max} (ng/mL)	14	409	419	313	131 (110,155)
	C_{tau} (ng/mL)	14	84	419	68	123 (109,138)

[a] Results from Phases 2 and 3 studies in adults with HIV receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

Key: AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; CI = confidence interval; C_{max} = maximum observed plasma concentration of drug; C_{tau} = observed drug concentration at the end of the dosing interval; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; ng = nanogram; TFV = tenofovir

EVG/c/FTC/TAF (Genvoya)

The PK of EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg as an FDC tablet have been evaluated in adolescents 12 to <18 years of age weighing ≥35 kg[14] and children 6 to <12 years of age weighing ≥25 kg.[17] AUC_{tau}, C_{max}, and C_{tau} for EVG, COBI, FTC, TAF, and TFV were comparable to or higher than those measured in adults with HIV in both cohorts (see Tables B and C below).

The PK of a low-dose FDC tablet containing EVG 90 mg, COBI 90 mg, FTC 120 mg, and TAF 6 mg were evaluated in 27 children with HIV weighing ≥14 kg and <25 kg.[21] EVG and TAF AUC_{tau} were higher in comparison to historical data in adults receiving full-strength Genvoya (see Tables B and C below). EVG C_{tau} was 21% lower (90% CI [53.1-117%]) in children versus adults but was approximately 4.4-fold higher and ninefold higher than the $PA\text{-}IC_{95}$ and $PA\text{-}IC_{50}$ for wild-type virus, respectively. However, EVG C_{tau} measured in this cohort was lower than those previously measured in children and adolescents weighing ≥25 kg with EVG at the 150-mg dose. COBI, FTC, and TFV exposures were all comparable to or higher than historical data in adults.

Table B. Pharmacokinetics of EVG, COBI, FTC, TAF, and TFV (Genvoya) in Children and Adolescents with HIV between 2 to <18 Years of Age and Weighing ≥14 kg

Component	Parameter	Children Aged ≥2 Years and Weighing ≥14 to <25 kg[21]		Children Aged 6 to <12 Years and Weighing ≥25 kg[17]		Adolescents Aged 12 to <18 Years and Weighing ≥35 kg[15]		Adults[a15,17]	
		n	GLSM	n	Mean (%CV)	n	Mean (%CV)	n	Mean (%CV)
EVG	AUC_{tau} (ng·h/mL)	27	29,900	22	33,814 (58%)	24	23,840 (26%)	19	22,800 (35%)
	C_{max} (ng/mL)	27	2,850	23	3,055 (39%)	24	2,230 (19%)	19	2,100 (34%)
	C_{tau} (ng/mL)	27	195	23	370 (119%)	24	301 (81%)	19	290 (62%)
COBI	AUC_{tau} (ng·h/mL)	27	12,300	20	15,891 (52%)	23	8,241 (36%)	19	9,500 (34%)
	C_{max} (ng/mL)	27	1,270	23	2,079 (47%)	24	1,202 (35%)	19	1,500 (28%)
	C_{tau} (ng/mL)	27	16.6	23	96 (169%)	15	25 (180%)	19	20 (85%)
FTC	AUC_{tau} (ng·h/mL)	27	18,600	22	20,629 (19%)	24	14,424 (24%)	19	11,714 (17%)
	C_{max} (ng/mL)	27	2,810	23	3,397 (27%)	24	2,265 (23%)	19	2,056 (20%)
	C_{tau} (ng/mL)	27	77.4	23	115 (24%)	23	102 (39%)	19	95 (47%)
TAF	AUC_{tau} (ng·h/mL)	27	344	23	333 (45%)	24	189 (56%)	539	206 (72%)
	C_{max} (ng/mL)	27	218	23	313 (61%)	24	167 (64%)	539	162 (51%)
TFV	AUC_{tau} (ng·h/mL)	27	327	23	440 (21%)	23	288 (19%)	841	293 (27%)
	C_{max} (ng/mL)	27	19.1	23	26 (21%)	23	18 (24%)	841	15 (26%)
	C_{tau} (ng/mL)	27	11.1	23	15 (25%)	23	10 (21%)	841	11 (29%)
TFV-DP in PBMCS	C_{0h} (fmol/10^6 cells)	—	—	—	—	12	222 (94%)	21	121 (91%)

[a] Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111.

Key: AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{0h} = concentration at time 0 (pre-dose); C_{max} = maximum observed plasma concentration of drug; C_{tau} = observed drug concentration at the end of the dosing interval; COBI = cobicistat; CV = coefficient of variation; EVG = elvitegravir; fmol = femtomole; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; ng = nanogram; PBMCs = peripheral blood mononuclear cells; TAF = tenofovir alafenamide; TFV = tenofovir; TFV-DP = tenofovir-diphosphate

Table C. Comparisons of EVG, COBI, FTC, TAF, and TFV (Genvoya) Pharmacokinetics in Children and Adolescents with HIV between 2 and <18 Years of Age and Weighing ≥14 kg to Adult Values

Component	Parameter	% GLSM (90% CI) Compared with Adult Values[a]			
		Dose (mg)	Children Aged ≥2 Years and Weighing ≥14 to <25 kg[17]	Dose (mg)	Children Aged 6 to <12 Years and Weighing ≥25 kg[21]
EVG	AUC_{tau} (ng·h/mL)	90	139 (112,172)	150	134 (104,173)
	C_{max} (ng/mL)		143 (113,180)		141 (115,173)
	C_{tau} (ng/mL)		79 (53,117)		86 (55,133)
COBI	AUC_{tau} (ng·h/mL)	90	—	150	158 (126,198)
	C_{max} (ng/mL)		—		127 (98,165)
	C_{tau} (ng/mL)		—		171 (95,310)
FTC	AUC_{tau} (ng·h/mL)	120	—	200	175 (160,192)
	C_{max} (ng/mL)		—		164 (145,184)
	C_{tau} (ng/mL)		—		125 (107,146)
TAF	AUC_{tau} (ng·h/mL)	6	193 (166,224)	10	171 (147,199)
	C_{max} (ng/mL)		150 (116,195)		182 (146,225)
TFV	AUC_{tau} (ng·h/mL)		—		152 (142,163)
	C_{max} (ng/mL)		—		173 (161,186)
	C_{tau} (ng/mL)		—		143 (132,155)

[a] Adult pharmacokinetic parameters for elvitegravir, cobicistat, and emtricitabine were derived from intensive pharmacokinetic analysis from Phase 2 study 102; data for tenofovir alafenamide and tenofovir were from population pharmacokinetic analyses in Phase 3 studies 104 and 111.

Key: AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; C_{max} = maximum observed plasma concentration of drug; COBI = cobicistat; C_{tau} = observed drug concentration at the end of the dosing interval; CI = confidence interval; EVG = elvitegravir; FTC = emtricitabine; GLSM = geometric least squares mean; kg = kilogram; mL = milliliter; mg = milligram; ng = nanogram; TAF = tenofovir alafenamide; TFV = tenofovir

Formulations

EVG is an integrase strand transfer inhibitor that is metabolized by CYP3A4. EVG must be used in the FDC products Stribild[3] or Genvoya,[6] both of which contain COBI (see below). COBI itself does not have ARV activity, but it is a CYP3A4 inhibitor that acts as a PK enhancer, similar to RTV.[22]

Coadministration of Elvitegravir, Cobicistat, and Darunavir

The combination of Stribild or Genvoya plus darunavir (DRV) may provide a low pill-burden regimen for antiretroviral therapy-experienced individuals. However, an unfavorable drug interaction between EVG/c and DRV is possible, and the available data on the magnitude of the interaction are conflicting. Data on the efficacy of the combination in adults also are conflicting.[23-29]

The most rigorous drug interaction study, performed in HIV-seronegative adults, found 21% lower DRV trough concentrations (C_{trough}) and 52% lower EVG C_{trough} with DRV 800 mg plus EVG/c 150 mg/150 mg once daily compared to the administration of either darunavir/cobicistat 800 mg/150 mg once daily or EVG/c 150 mg/150 mg once daily alone.[23] The actual C_{trough} were 1,050 ng/mL for DRV and 243 ng/mL for EVG.

Despite the findings of the aforementioned drug interaction study in HIV-seronegative adults, the most rigorous efficacy evaluation found that among 89 treatment-experienced adults who were receiving five-tablet ARV regimens, 96.6% achieved virologic suppression (HIV RNA <50 copies/mL) 24 weeks after simplifying their regimens to a two-tablet regimen of Genvoya plus DRV 800 mg once daily.[27] Intensive PK sampling was performed in 15 of these patients (17%). Mean DRV and EVG C_{trough} were 1,250 ng/mL and 464 ng/mL, respectively.

Given the uncertainty around the true magnitude of the drug interaction and the absence of data in children, this combination should be used with caution in children.

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Raltegravir (RAL, Isentress)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations

Tablet: 400 mg (film-coated poloxamer tablet)

High-Dose (HD) Tablet: 600 mg (film-coated poloxamer tablet)

Chewable Tablets: 100 mg (scored) and 25 mg

Granules for Oral Suspension: Single-use packet of 100 mg of raltegravir, suspended in 10 mL of water for a final concentration of 10 mg/mL

Film-coated tablets, chewable tablets, and oral suspension are not interchangeable.

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Note: No dosing information is available for preterm infants or infants weighing <2 kg at birth. See Table 12 in Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection for information about using raltegravir (RAL) for the prevention of perinatal HIV transmission.

Neonate (Weighing ≥2 kg) Dose[a]

Raltegravir Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks

Neonates Aged ≥37 Weeks and Weighing ≥2 kg

Weight	Volume (Dose) of Suspension
Birth to 1 Week of Age: Once-Daily Dosing	**Approximately 1.5 mg/kg per dose**
2 kg to <3 kg	0.4 mL (4 mg) once daily
3 kg to <4 kg	0.5 mL (5 mg) once daily
4 kg to <5 kg	0.7 mL (7 mg) once daily
1–4 Weeks of Age: Twice-Daily Dosing	**Approximately 3 mg/kg per dose**
2 kg to <3 kg	0.8 mL (8 mg) twice daily
3 kg to <4 kg	1 mL (10 mg) twice daily
4 kg to <5 kg	1.5 mL (15 mg) twice daily

[a] RAL is metabolized by uridine diphosphate glucuronyl transferase (UGT) 1A1, and enzyme activity is low at birth; enzyme activity increases rapidly during the next 4–6 weeks of life.

Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache, dizziness, fatigue
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

Special Instructions

- RAL can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any RAL formulations.
- Significant drug interactions are more likely to occur when the RAL HD formulation is used once daily. **The following drugs should not be coadministered with once-daily RAL HD dosing:** calcium carbonate antacids, rifampin, tipranavir/ritonavir, and etravirine.
- Chewable tablets can be chewed, crushed (before administration), or swallowed whole.
- Film-coated tablets, including HD tablets, must be swallowed whole.
- The chewable tablets and oral suspension have better bioavailability than the film-coated tablets. Because the formulations are not interchangeable, **do not substitute** chewable tablets or oral suspension for film-coated

Note: If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose should be delayed until 24–48 hours after birth.

Infant >4 Weeks of Age and Child (Weighing ≥3 kg to <20 kg) Dose

- For children weighing 3–20 kg, either oral suspension or chewable tablets can be used.

Raltegravir Oral Suspension Dosing Table for Patients Aged >4 Weeks[a]

Note: The maximum dose of oral suspension is 10 mL (RAL 100 mg) twice daily.

Weight	Twice-Daily Volume (Dose) of Suspension
3 kg to <4 kg	2.5 mL (25 mg) twice daily
4 kg to <6 kg	3 mL (30 mg) twice daily
6 kg to <8 kg	4 mL (40 mg) twice daily
8 kg to <10 kg	6 mL (60 mg) twice daily
10 kg to <14 kg	8 mL (80 mg) twice daily
14 kg to <20 kg	10 mL (100 mg) twice daily

[a] The weight-based dose recommendation for the oral suspension is based on a dose of approximately RAL 6 mg/kg per dose twice daily.

Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

Children Weighing ≥3 kg

- Weighing <25 kg
    - Chewable tablets twice daily. See the table below for chewable tablet doses.
- Weighing ≥25 kg
    - RAL 400-mg, film-coated tablets twice daily **or** chewable tablets twice daily. See the table below for chewable tablet doses.

Children and Adolescents Weighing ≥40 kg

- Two RAL 600-mg HD tablets (1,200 mg) once daily
- This dose is for antiretroviral therapy-naive or virologically suppressed patients who are on an initial dose of RAL 400 mg twice daily.

Chewable Tablet Dosing Table[a]

Note: The maximum dose of chewable tablets is RAL 300 mg twice daily.

tablets. See specific recommendations for proper dosing of different formulations.

- The chewable tablets should be stored in the original package with a desiccant to protect them from moisture.
- **Instructions for preparing and administering the chewable tablet as a crushed tablet are as follows:** Place the tablet(s) in a small, clean cup. For each tablet, add a teaspoon (~5 mL) of liquid (e.g., water, juice, or breast milk). Within 2 minutes, the tablet(s) will absorb the liquid and fall apart. Using a spoon, crush any remaining pieces of the tablet(s). Immediately administer the entire dose orally. If any portion of the dose is left in the cup, add another teaspoon (~5 mL) of liquid, swirl, and administer immediately.
- The chewable tablets contain phenylalanine, a component of aspartame. Phenylalanine can be harmful to patients with phenylketonuria, and the necessary dietary adjustments should be made in consultation with a metabolic specialist.
- The oral suspension comes in a kit that includes instructions for use, mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document. Each single-use foil packet contains 100 mg of RAL, which will be suspended in 10 mL of water for a final concentration of RAL 10 mg/mL. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension.
- **Do not shake the oral suspension.** Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document. For neonates, most of the prepared oral suspension will be discarded, because the volume for the required dose is much smaller than 10 mL.

Metabolism/Elimination

- UGT1A1-mediated glucuronidation

Raltegravir Dosing in Patients with Hepatic Impairment

- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving RAL twice daily.
- No studies have been conducted on the use of RAL HD in patients with hepatic impairment. Therefore, administering RAL HD **is not recommended** in patients with hepatic impairment.
- The effect of severe hepatic impairment on RAL pharmacokinetics has not been studied.

Weight	Twice-Daily Dose	Number of Chewable Tablets
3 kg to <6 kg	RAL 25 mg	1 tablet (25 mg)
6 kg to <10 kg	RAL 50 mg	2 tablets (25 mg)
10 kg to <14 kg	RAL 75 mg	3 tablets (25 mg)
14 kg to <20 kg	RAL 100 mg	1 tablet (100 mg)
20 kg to <28 kg	RAL 150 mg	1½ tablets[b] (100 mg)
28 kg to <40 kg	RAL 200 mg	2 tablets (100 mg)
≥40 kg	RAL 300 mg	3 tablets (100 mg)

[a] The weight-based dose recommendation for the chewable tablet is based on a dose of approximately RAL 6 mg/kg per dose twice daily.

[b] The RAL 100-mg chewable tablet can be divided into equal halves.

Raltegravir Dosing in Patients with Renal Impairment

- No dose adjustment is necessary in patients with any degree of renal impairment.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* The major route of raltegravir (RAL) elimination is mediated through glucuronidation by uridine diphosphate glucuronyl transferase (UGT) 1A1.
- Coadministering RAL with inducers of UGT1A1—such as rifampin and tipranavir—may result in reduced plasma concentrations of RAL. Inhibitors of UGT1A1—such as atazanavir (ATV)—may increase plasma concentrations of RAL. No dosing modifications are recommended when RAL is coadministered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r). However, RAL high-dose (HD) tablets **should not be coadministered** with TPV/r.
- In adults, an increased dose of RAL is recommended when it is coadministered with rifampin. For adults receiving rifampin, the recommended RAL dose is 800 mg twice daily. **Do not coadminister** rifampin with once-daily RAL HD tablets. In children aged 4 weeks to <12 years who had tuberculosis (TB)/HIV coinfection and were taking rifampin, RAL 12 mg/kg per dose twice daily of the chewable tablet formulation safely achieved pharmacokinetic (PK) targets.[1,2]
- Aluminum-containing antacids and magnesium-containing antacids may reduce RAL plasma concentrations and **should not be coadministered** with RAL.
- Significant drug interactions may be more likely to occur with RAL HD once daily. Trough concentration (C_{trough}) in adults is approximately 30% lower with RAL HD 1,200 mg once daily than with RAL 400 mg twice daily. A lower C_{trough} increases the potential for clinically significant drug interactions with interfering drugs that decrease RAL exposure and further lower C_{trough}. In addition to aluminum-containing and magnesium-containing antacids, the following drugs **should not be coadministered** with the RAL HD formulation: calcium carbonate antacids, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug-metabolizing enzymes on RAL is unknown; coadministration with phenytoin, phenobarbital, and carbamazepine **is not recommended**.

- Before administering RAL, clinicians should carefully review a patient's medication profile for potential drug interactions with RAL.

Major Toxicities

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, itching, insomnia.
- *Less common:* Abdominal pain, vomiting. Patients with chronic active hepatitis B virus infection and/or hepatitis C virus infection are more likely to experience a worsening adverse events (AEs) grade from baseline for laboratory abnormalities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than patients who are not coinfected.
- *Rare:* Moderate-to-severe increase in creatine phosphokinase levels. Use RAL with caution in patients who are receiving medications that are associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with a history of these conditions. Rash (including Stevens-Johnson syndrome), hypersensitivity reaction, and toxic epidermal necrolysis. Thrombocytopenia. Cerebellar ataxia. Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications.

Resistance

The International AIDS Society–USA maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

RAL is an integrase strand transfer inhibitor that is approved by the U.S. Food and Drug Administration (FDA) for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV in pediatric patients weighing ≥2 kg. The current pediatric FDA approval and dose recommendations are based on evaluations of 122 patients aged ≥4 weeks to 18 years who participated in IMPAACT P1066 and 42 full-term neonates who were treated for ≤6 weeks starting from birth and followed for a total of 24 weeks during IMPAACT P1110.[3]

The FDA has approved RAL HD, which allows once-daily dosing, for use in children and adolescents weighing ≥40 kg.

Efficacy in Clinical Trials

RAL has been evaluated in adults in three large, randomized clinical trials: STARTMRK, SPRING-2, and ACTG A5257. STARTMRK compared the safety and efficacy of a RAL-containing regimen and an efavirenz (EFV)-containing regimen. At 48 weeks, RAL was noninferior to EFV. However, more patients discontinued EFV during the longer follow-up periods of 4 and 5 years, and RAL was found to be virologically and immunologically superior to EFV.[4-6] Results from the SPRING-2 study in treatment-naive adults showed that RAL and dolutegravir (DTG) were equally effective and had similar safety profiles.[7] ACTG A5257 compared RAL to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but RAL had better tolerability.[8] The ONCEMRK study compared RAL 1,200 mg once daily (taken as two 600-mg RAL HD tablets) to RAL 400 mg twice daily in treatment-naive adults (see the results for the ONCEMRK study in the following section). Once-daily dosing of RAL using the HD tablets was approved by the FDA for adults and children weighing ≥40 kg who are either treatment naive or virologically suppressed on a twice-daily RAL regimen.

RAL was studied in infants, children, and adolescents in IMPAACT P1066, an open-label trial that evaluated PKs, safety, tolerability, and efficacy. In 96 participants aged 2 to 18 years who were mostly antiretroviral therapy (ART) experienced, 79.1% of the patients achieved a favorable viral load response (i.e., viral loads <400 copies/mL or ≥1 $\log_{10}$ decline in viral load) while receiving the currently recommended dose of RAL. Infants and toddlers aged ≥4 weeks to <2 years also were enrolled in IMPAACT P1066 and received treatment with RAL oral suspension. At Weeks 24 and 48, 61% of the participants (14 of 23 infants and toddlers) had HIV viral loads[9-11] <400 copies/mL.

Efficacy and Pharmacokinetics of Once-Daily Dosing in Children and Adults

RAL PKs exhibit considerable intrasubject and intersubject variability.[12,13] Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naive patients with HIV were randomized to receive RAL 800 mg once daily or RAL 400 mg twice daily. After 48 weeks of treatment, the percent of patients who achieved HIV RNA viral loads <50 copies/mL was 83% in the once-daily group, compared with 89% in the twice-daily group. Patients in the once-daily arm with C_{trough} concentrations <45 nM (20 ng/mL) were at greater risk of experiencing treatment failure.[12,13] Overall drug exposures were similar in both groups, but the association between higher risk of treatment failure and lower C_{trough} concentrations suggests that maintaining RAL trough plasma concentrations >45 nM (20 ng/mL) is important for efficacy.[12,13]

Once-daily dosing with RAL 1,200 mg was found to be as effective as dosing with RAL 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either RAL 1,200 mg once daily (taken as two 600-mg tablets) or RAL 400 mg twice daily plus tenofovir disoproxil fumarate plus emtricitabine. After 48 weeks, 89% of participants on the once-daily dose and 88% of participants on the twice-daily dose reached viral loads of <40 copies/mL. Discontinuation rates due to AEs were not different between the two groups.[14] In May 2017, once-daily dosing of RAL using the HD tablets was approved by the FDA for adults and children weighing ≥40 kg who are either treatment naive or virologically suppressed on a twice-daily RAL regimen. The use of once-daily dosing with the HD tablets has not been studied in pediatric patients. Population PK modeling and simulations of once-daily dosing with RAL HD tablets predict that this dosing schedule will produce drug exposures similar to those observed in adult patients during ONCEMRK.[3,15]

Dosing with three 400-mg RAL tablets once daily and dosing with two 600-mg RAL HD tablets once daily are expected to produce similar PK profiles. In adults enrolled in ONCEMRK, the C_{trough} concentrations were approximately 30% lower in participants taking once-daily RAL HD tablets than in those taking RAL 400 mg twice daily. Because of this, once-daily dosing of RAL has a greater potential for significant drug interactions; coadministering once-daily RAL with drugs that decrease drug exposure may further decrease C_{trough}. The highest concentration (C_{max}) is approximately six times higher in patients receiving RAL 1,200 mg once daily than in those receiving RAL 400 mg twice daily, with a twofold higher area under the curve (AUC).

Although modeling and simulations for pediatric patients indicate that PK targets are met using the once-daily RAL 1,200-mg dose, no clinical data exist on the use of this dose in children weighing

<50 kg. Six children in IMPAACT P1066 had drug exposures that were similar to those observed in ONCEMRK, but all six children weighed >50 kg. Dose-related central nervous system toxicities—such as insomnia or hyperactivity—may occur in children who are exposed to very high concentrations of RAL.[3]

Efficacy and Pharmacokinetics in Children

IMPAACT P1066 evaluated the PKs, safety, and efficacy of RAL in treatment-experienced children aged 4 weeks to 18 years. A summary of RAL steady-state PK parameters, following administration of the recommended twice-daily doses (approximately 6 mg/kg twice daily), can be found in Table A below.[10,11]

Table A. Raltegravir Steady-State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Twice-Daily Doses: IMPAACT P1066

Body Weight	Formulation	Dose	N*	Geometric Mean (% CV†) AUC_{0-12h} (µM●h)[a,b]	Geometric Mean (% CV†) C_{12h} (nM)[a,b]
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (121%)	233 (157%)
≥25 kg	Chewable tablet	Weight-based dosing[c]	9	22.1 (36%)	113 (80%)
11 kg to <25 kg	Chewable tablet	Weight-based dosing[c]	13	18.6 (68%)	82 (123%)
3 kg to <20 kg	Oral suspension	Weight-based dosing[c]	19	24.5 (43%)	113 (69%)
* Number of patients with intensive PK results at the final recommended dose † Geometric coefficient of variation					

[a] Pharmacokinetic targets for film-coated tablets and chewable tablets: $AUC_{0–12h}$ 14–25 µM·h (6–11 mg·h/L); C_{12h} nM ≥33 nM (14.7 ng/mL)

[b] Pharmacokinetic targets for oral suspension: $AUC_{0–12h}$ 14–45 µM·h (6–20 mg·h/L); C_{12h} nM ≥75 nM (33.3 ng/mL)

[c] To approximate 6 mg/kg twice daily

Key: AUC = area under the curve; $AUC_{0–12h}$ = AUC from time zero to 12 hours after drug administration; C_{12h} = concentration at 12 hours (trough); CV = coefficient of variation

Children Aged 2 Years to 18 Years

IMPAACT P1066 was a Phase 1/2 open-label, multicenter study that evaluated the PK profile, safety, tolerability, and efficacy of various formulations of RAL in ART-experienced children and adolescents with HIV aged 2 to 18 years. RAL was administered in combination with an optimized background ARV regimen.[11,16] Subjects received either the RAL 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing ≥25 kg) or the chewable tablet formulation at a dose of RAL 6 mg/kg twice daily (patients aged 2 years to <12 years). In IMPAACT P1066, the initial dose-finding stage included an intensive PK evaluation in various age cohorts (Cohort 1: 12 years to <19 years; Cohort 2: 6 years to <12 years; Cohort 3: 2 years to <6 years). Doses were selected with the aim of achieving target PK parameters that were similar to those seen in adults: PK targets were a geometric mean (GM) $AUC_{0–12h}$ of 14 µM·h to 25 µM·h and a GM 12-hour concentration (C_{12h}) >33 nM. Additional participants were then enrolled in each age cohort to evaluate the long-term efficacy, tolerability, and safety of RAL.

A total of 126 treatment-experienced participants were enrolled, with 96 participants receiving the final recommended dose of RAL. Only treatment-experienced patients were eligible to enroll, and the optimized regimen was determined by the site investigators. Adolescents tended to be more treatment experienced and have more advanced disease than those in the younger cohorts, with 75% having the Centers for Disease Control and Prevention Category B or C classification of HIV infection. Ninety-six participants completed 48 weeks of treatment. Seventy-nine percent of participants achieved HIV RNA <400 copies/mL, and 57% of participants achieved HIV RNA <50 copies/mL, with a mean CD4 T lymphocyte (CD4) count increase[11] of 156 cells/mm^3 (4.6%). Among 36 subjects who experienced virologic failure, the development of drug resistance and/or poor adherence were contributing factors. Genotypic resistance data were available for 34 patients who experienced virologic failure, and RAL-associated mutations were detected in 12 out of 34 of those patients. The frequency, type, and severity of AEs through Week 48 were comparable to those observed in adult studies. AEs were commonly reported, but few serious AEs were considered to be drug related. Patients with AEs that were considered to be drug related included one patient with Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia, as well as one patient with a Grade 2 allergic rash on Day 17 and Grade 3 ALT and Grade 4 AST laboratory elevations after Day 122. There were no discontinuations due to AEs and no drug-related deaths.[11] Overall, RAL was well tolerated when administered as a film-coated tablet twice daily in subjects aged 6 years to <19 years and as chewable tablets at a dose of approximately 6 mg/kg twice daily in subjects aged 2 years to <12 years, with favorable virologic and immunologic responses.[17]

Children Aged ≥4 Weeks to <2 Years

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the granules for RAL oral suspension in combination with an optimized background ARV regimen. All subjects had previously received ARV drugs to prevent perinatal transmission and/or treat HIV, and 69% had baseline plasma HIV RNA exceeding 100,000 copies/mL. PK targets for Cohort IV (6 months to <2 years) and Cohort V (4 weeks to <6 months) were modified to a GM $AUC_{0–12h}$ of 14 µM·h to 45 µM·h and a GM C_{12h} ≥75 nM (33.3 ng/mL). These targets were modified so that an estimated >90% of patients would have C_{12h} above the 45 nM threshold. By Week 48, two subjects experienced AEs that were thought to be related to the study drug: one patient experienced a serious erythematous rash that resulted in permanent discontinuation of RAL, and one patient experienced immune reconstitution inflammatory syndrome. Virologic success, defined as ≥1 $\log_{10}$ decline in HIV RNA or <400 copies/mL at 48 weeks, was achieved in >87% of participants. At 48 weeks of follow up, 45.5% of subjects had HIV RNA <50 copies/mL and mean CD4 count increases of 527.6 cells/mm^3 (7.3%). Four subjects in Cohort 4 experienced virologic failure by Week 48, and one participant had a RAL-associated resistance mutation. Overall, the granules for oral suspension, at a dose of approximately RAL 6 mg/kg twice daily, were well tolerated and had good efficacy.[10]

Long-Term Follow Up in Children

The IMPAACT P1066 study team reported results regarding the safety and efficacy of different RAL formulations at 240 weeks in children enrolled in this multicenter trial.[18] Eligible participants were children aged 4 weeks to 18 years who had previously been treated with ART and who were experiencing virologic failure at the time of enrollment. RAL was added to an optimized ARV regimen in all participants. RAL was well tolerated, and few serious clinical or laboratory safety events were noted during the study.[18]

The proportion of participants who achieved virologic success at 240 weeks varied by the RAL formulation used: 19 of 43 children (44.2%) who received RAL 400-mg tablets; 24 of 31 children (77.4%) who received chewable tablets; and 13 of 15 children (86.7%) who received the oral granules for suspension. RAL resistance was documented in 19 of 50 patients (38%) who experienced virologic rebound after initial suppression. These results suggest that younger children with less treatment experience are more likely to have sustained virologic suppression, whereas older children with an extensive treatment history are more likely to experience treatment failure and develop resistance to RAL. Poor adherence among adolescents may have contributed to the lower efficacy observed in older children who received the RAL 400-mg tablets.[18]

Neonates Aged <4 Weeks

RAL is metabolized by UGT1A1, the same enzyme that is responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. Washout PKs of RAL in neonates born to pregnant women with HIV were studied in IMPAACT P1097.[19] The neonatal plasma half-life of RAL was highly variable, ranging from 9.3 to 184 hours. This suggests that neonatal development may impact UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of RAL. RAL competes with unconjugated bilirubin for albumin binding sites. When RAL plasma concentrations are extremely high, unconjugated bilirubin may be displaced from albumin by RAL and cross the blood–brain barrier, leading to bilirubin-induced neurologic dysfunction. The effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant, unless concentrations that are 50-fold to 100-fold higher than typical peak concentrations are reached (approximately 5,000 ng/mL).[20]

IMPAACT P1110 was a Phase 1, multicenter trial that enrolled full-term neonates with or without *in utero* RAL exposure at risk of acquiring HIV. RAL-exposed neonates were those whose mothers received RAL within 2 to 24 hours of delivery. For RAL-exposed neonates, the initial dose of RAL was delayed until 12 to 60 hours after delivery. The study design included two cohorts: Cohort 1 infants received two RAL doses that were administered 1 week apart, and Cohort 2 infants received daily RAL doses for the first 6 weeks of life. PK data from Cohort 1 and from older infants and children were combined in a population PK model, and simulations were used to select the following RAL dosing regimen for evaluation in infants in Cohort 2: RAL 1.5 mg/kg daily, starting within 48 hours of life and continuing through Day 7; RAL 3 mg/kg twice daily on Days 8 to 28 of life; and RAL 6 mg/kg twice daily after 4 weeks of age.[21] Protocol exposure targets for each subject were $AUC_{0–24hr}$ 12 mg·h/L to 40 mg·h/L, $AUC_{0–12hr}$ 6 mg·h/L to 20 mg·h/L, and C_{12h} or C_{24h} >33 ng/mL. Safety was assessed using clinical and laboratory evaluations.[19,22,23]

Twenty-six RAL-naive infants and 10 RAL-exposed infants were enrolled in Cohort 2; 25 RAL-naive infants and 10 RAL-exposed infants had evaluable PK results and safety data. Results for the RAL-naive infants and RAL-exposed infants who were enrolled in Cohort 2 are contained in Table B below.[23]

Table B. Raltegravir Pharmacokinetic Parameters for Raltegravir-Naive and Raltegravir-Exposed Neonates

PK Parameter	Initial Dose: RAL 1.5 mg/kg Once Daily RAL-Naive (n = 25)[d]	Initial Dose: RAL 1.5 mg/kg Once Daily RAL-Exposed (n = 10)	Days 15–18: RAL 3.0 mg/kg Twice Daily RAL-Naive (n = 24)[e]	Days 15–18: RAL 3.0 mg/kg Twice Daily RAL-Exposed (n = 10)[f]
	GM (CV%)	GM (CV%)	GM (CV%)	GM (CV%)
$AUC_{0–24h}$ (mg·h/L)[a]	38.2 (42.0%)	42.9 (25.3%)	_	_
$AUC_{0–12h}$ (mg·h/L)	_	_	14.3 (49.5%)	18.3 (62.8%)
C_{trough} (ng/mL)[b]	948 (84.0%)	946 (74.0%)	176 (162.1%)	274 (176.4%)
C_{max} (ng/mL)[c]	2,350 (36.5%)	2,565 (23.1%)	2,849 (47.5%)	3,667 (46.3%)
T_{max} (hours)	5.4 (71.5%)	3.8 (88.8%)	2.3 (77.1%)	1.9 (52.3%)
$T_{1/2}$ (hours)	15.8 (101.4%)	14.4 (69.5%)	2.5 (34.1%)	2.9 (20.7%)

[a] AUC targets: $AUC_{0–24h}$ 12–40 mg·h/L and $AUC_{0–12h}$ 6–20 mg·h/L.

[b] C_{trough} concentration >33 ng/mL. For initial dose, C_{last} collected at 24 hours was used. For Days 15–18, C_{12h} was estimated when the 12 hours post-dose sample was collected earlier than 12 hours after dosing (the protocol specified a sample collection time of 8–12 hours post dose).

[c] C_{max} <8,724 ng/mL

[d] $AUC_{0–24h}$ could not be estimated for one infant.

[e] $AUC_{0–12h}$ and C_{trough} could not be estimated for one infant with delayed absorption.

[f] $AUC_{0–12h}$ and C_{max} could not be estimated for one infant with incomplete sample collection.

Key: AUC = area under the curve; $AUC_{0–12h}$ = AUC from time zero to 12 hours after drug administration; $AUC_{0–24h}$ = AUC from time zero to 24 hours after drug administration; C_{last} = last measurable plasma concentration; C_{max} = maximum concentration; C_{trough} = trough concentration; CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic; RAL = raltegravir; $T_{1/2}$ = half-life; T_{max} = time to reach maximum concentration

Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for up to 6 weeks from birth and followed for a total of 24 weeks. All GM protocol exposure targets were met. In some infants, $AUC_{0–24h}$ following the initial dose was slightly above the target range, but this is considered acceptable given the rapid increase in RAL metabolism during the first week of life. The PK targets and the safety guidelines were met for both RAL-naive and RAL-exposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory AEs were reported among the RAL-naive infants: Grade 4 transient neutropenia occurred in one infant who received a zidovudine-containing regimen; two bilirubin elevations (one Grade 1 and one Grade 2) were considered nonserious and did not require specific therapy.[3] Among the RAL-exposed infants, four infants exhibited Grade 3 or 4 toxicities: anemia in one infant, neutropenia in one infant, and hyperbilirubinemia in two infants. No specific therapy was required to treat these toxicities, and no infants required phototherapy or exchange transfusion for hyperbilirubinemia.

Results from IMPAACT P1110 confirmed the PK modeling and simulation submitted for FDA approval and labeling. Neonates born to mothers who received RAL 2 to 24 hours prior to delivery should have their first dose of RAL delayed until 24 to 48 hours after birth.[22,23] RAL can be safely administered to full-term infants using the daily dosing regimen that was studied in IMPAACT P1110. This regimen **is not recommended** for use in preterm infants.

RAL elimination kinetics in preterm and low-birth-weight neonates after maternal dosing was studied in IMPAACT P1097.[24] Sixteen mothers and their 18 low-birth-weight neonates (<2.5 kg) were enrolled. Median (range) RAL elimination half-life was 24.4 hours (10.1–83) hours (n = 17). A PK model incorporating slower clearance in preterm neonates demonstrated that a reduction in RAL dosing is required in this population.[24]

Two case reports of preterm infants who received RAL to prevent perinatal transmission have been published.[25,26] These case reports involved one infant born at a gestational age of 24 weeks and 6 days who weighed 800 g and another infant born at 33 weeks gestation who weighed 1,910 g. In both infants, intermittent dosing of RAL was done using real-time therapeutic drug monitoring in the neonatal intensive care unit.[25,26] Less frequent dosing was required because RAL elimination was significantly delayed in these preterm infants. RAL PKs and safety must be studied in preterm infants before RAL can be safely used without real-time PK monitoring in this population.

Formulations

The PKs of RAL in adult patients with HIV who swallowed intact 400-mg tablets were compared with those observed in patients who chewed the 400-mg, film-coated tablets because of swallowing difficulties. Drug absorption was significantly higher among patients who chewed the tablets, although the palatability was rated as poor.[27] In adult volunteers, the PKs of RAL 800 mg taken once daily by chewing was compared with the PKs of two doses of RAL 400 mg taken every 12 hours by swallowing. Participants who took RAL by chewing had significantly higher drug exposure and reduced PK variability than those who swallowed whole tablets according to current recommendations.[28] According to the manufacturer, the film-coated tablets must be swallowed whole.

The RAL chewable tablet and oral suspension have higher oral bioavailability than the 400-mg, film-coated tablet, according to a comparative study in healthy adult volunteers.[29] Compared with the RAL 400-mg tablet formulation, the RAL 600-mg tablet has higher relative bioavailability.[3,30] Interpatient and intrapatient variability for PK parameters of RAL are considerable, especially with the film-coated tablets.[3,31] Because of differences in the bioavailability of various formulations, the dosing recommendations for each formulation differ, and the formulations **are not interchangeable.** When prescribing RAL, clinicians should refer to the appropriate dosing table for the chosen formulation. The use of RAL chewable tablets as dispersible tablets in children aged <2 years has been studied in IMPAACT P1101 for infants and toddlers with TB/HIV coinfection who received rifampin as part of their TB treatment. The use of RAL chewable tablets dispersed in water at a dose of RAL 12 mg/kg per dose twice daily safely achieved PK targets.[1,32] The RAL chewable tablets are now approved for use in infants and young children 4 weeks of age and older and weighing at least 2 kg.[33] An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including water, apple juice, and breast milk.[33] The chewable tablets may be crushed and mixed with a small amount of liquid to facilitate administration (see Special Instructions above).

Palatability was evaluated as part of IMPAACT P1066. Both chewable tablets and oral granules for suspension were thought to have acceptable palatability. Seventy-three percent of those surveyed reported no problems with chewable tablets; 82.6% reported no problems with administering the oral granules.[10,11] The acceptability and feasibility of administering RAL granules for oral suspension in a low-resource setting has been studied in a clinic in South Africa. With proper training by health care personnel, caregivers were able to prepare the suspension safely and accurately.[34]

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Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

Cobicistat (COBI, Tybost)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Tablet: 150 mg **Fixed-Dose Combination (FDC) Tablets** • [Evotaz] Atazanavir 300 mg/cobicistat 150 mg • [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg • [Prezcobix] Darunavir 800 mg/cobicistat 150 mg • [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg • [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg When using FDC tablets, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Cobicistat Is a Pharmacokinetic Enhancer • The only use of cobicistat (COBI) is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase strand transfer inhibitors. COBI **is not interchangeable** with ritonavir (RTV) and has no antiviral activity. **Child and Adolescent (Weighing ≥35 kg) and Adult Dose** • COBI 150 mg with atazanavir (ATV) 300 mg administered at the same time with food **Child and Adolescent (Weighing ≥40 kg) and Adult Dose** • COBI 150 mg with darunavir (DRV) 800 mg administered at the same time with food **[Evotaz] Atazanavir/Cobicistat** *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* • One tablet once daily with food • Use in combination with other antiretroviral (ARV) drugs.	• COBI is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate, with no change in glomerular function. **Special Instructions** • COBI 150 mg **is not interchangeable** with RTV, but it has a PK boosting effect that is comparable to RTV 100 mg. • Drug interactions may differ between RTV and COBI, because COBI is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of RTV. • **Do not administer** COBI with RTV or with FDC tablets that contain COBI. • COBI **is not recommended** for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI). • Using COBI with PIs other than once-daily ATV 300 mg or DRV 800 mg **is not recommended.** • Patients with a confirmed increase in serum creatinine >0.4 mg/dL from baseline should be closely monitored for renal safety. • When using COBI in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while the patient is receiving therapy (see Table 15i.

[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF) *Child (Weighing ≥14 to <25 kg)* • Limited data currently exist on the appropriate dose of Genvoya in children ≥14 kg to <25 kg. Studies are currently being conducted to assess the safety and efficacy of a low-dose tablet with elvitegravir (EVG) 90 mg/COBI 90 mg/emtricitabine (FTC) 120 mg/TAF 6 mg. *Child and Adolescent (Weighing ≥25 kg) and Adult Dose* • One tablet once daily with food **[Prezcobix] Darunavir/Cobicistat** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose* • One tablet once daily with food • Use in combination with other ARV drugs. **[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)** *Child and Adolescent (Weighing ≥35 kg) and Adult Dose* • One tablet once daily with food • The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends using Stribild only in patients with sexual maturity ratings of 4 or 5. **[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose* • One tablet once daily with food	Nephrotoxic Effects). In patients who are at risk of renal impairment, serum phosphate also should be monitored. • For information on crushing and cutting tablets, see this table from Toronto General Hospital. **Metabolism/Elimination** • COBI is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6. **Cobicistat Dosing in Patients with Hepatic Impairment** • COBI does not require dose adjustment in patients with mild-to-moderate hepatic impairment. No data are available in patients with severe hepatic impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.[1] • Genvoya, Prezcobix, Stribild, and Symtuza **are not recommended** in patients with severe hepatic impairment.[1] • Evotaz **is not recommended** in patients with any degree of hepatic impairment. **Cobicistat Dosing in Patients with Renal Impairment** • COBI does not require a dose adjustment in patients with renal impairment, including those with severe renal impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.[1] • The use of COBI plus TDF **is not recommended** in patients with creatinine clearance (CrCl) <70 mL/min. Dose adjustments for TDF are required for patients with CrCl <50 mL/min, and the necessary dose adjustments for TDF when this drug is used with COBI have not been established in this group of patients.[1] • Stribild[2] **should not be initiated** in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min. The dose adjustments required for emtricitabine and TDF in these patients cannot be achieved with an FDC tablet. • Genvoya[3] and Symtuza[4] **are not recommended** in patients with estimated CrCl <30 mL/min.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Metabolism of cobicistat (COBI) is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. COBI also inhibits breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1 (MATE1). Unlike ritonavir (RTV), COBI does not demonstrate any enzyme-inducing effects. The potential exists for multiple drug interactions when using COBI. Before COBI is administered, a patient's medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs. Coadministration of medications that induce or inhibit CYP3A4 may respectively decrease or increase exposures of COBI and coformulated antiretroviral medications. Coadministration of medications that are CYP3A4 substrates may result in clinically significant adverse reactions that are severe, life-threatening, or fatal, or may result in loss of therapeutic effect if dependent on conversion to an active metabolite due to CYP3A4 inhibition by COBI.[1]

- *Nucleoside reverse transcriptase inhibitors:* COBI is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with COBI produces tenofovir (TFV) exposures that are similar to those produced by TAF 25 mg without COBI.[5] COBI increases plasma TFV exposures by 23% when it is coadministered with TDF; thus, renal safety should be monitored in patients who are receiving this combination.[1,6]
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine **should not be used** with COBI.
- *Protease inhibitors:* Using COBI as a dual booster for elvitegravir (EVG) and darunavir (DRV) has been studied in people with HIV and people without HIV, and the evidence is conflicting. When EVG plus COBI plus DRV was administered to people without HIV, the trough concentration (C_{trough}) of EVG was 50% lower than the C_{trough} seen in people who received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) without DRV.[7] When EVG/c/FTC/TAF was administered with DRV to patients with HIV, both DRV and EVG concentrations were comparable to those seen in historic controls.[8]
- *Integrase inhibitors:* In one small study, dolutegravir (DTG) C_{trough} was 107% higher when DTG was administered with darunavir/cobicistat (DRV/c) than when it was administered with darunavir/ritonavir.[9] Bictegravir (BIC) area under the curve increases 74% when BIC is administered with DRV/c.[10]
- *Corticosteroids:* Increased serum concentrations of corticosteroids can occur when corticosteroids and COBI are coadministered; this can lead to clinically significant adrenal suppression. Adrenal suppression occurs regardless of whether the corticosteroids are administered orally or by some other route (e.g., intranasal, inhaled, interlaminar, intraarticular) and regardless of whether the corticosteroids are administered routinely or intermittently. A possible exception is beclomethasone, which appears to be a relatively safe option with inhaled or intranasal administration.[11,12]

Major Toxicities

- *More common:* Nausea, vomiting, diarrhea, abdominal pain, anorexia
- *Less common (more severe):* New onset renal impairment or worsening of renal impairment when used with TDF. Rhabdomyolysis; increased amylase and lipase levels.

Resistance

Not applicable because COBI has no antiviral activity.

Pediatric Use

Approval

COBI is a pharmacokinetic (PK) enhancer of antiretroviral drugs that is available as a single agent or a component of fixed-dose combination (FDC) products. COBI, as a component of Stribild, is approved by the

U.S. Food and Drug Administration (FDA) at the adult dose for use in children and adolescents aged ≥12 years and weighing ≥35 kg. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting the use of Stribild to those with a sexual maturity rating of 4 or 5. COBI, as a component of Genvoya, is approved by the FDA at the adult dose for use in children weighing ≥25 kg. The FDA has not approved COBI as a component of Genvoya for use in children <25 kg, but an ongoing PK, safety, and efficacy study is underway with a low-dose tablet in children weighing ≥14 kg to <25 kg (see the Elvitegravir section). COBI alone (as Tybost) is approved by the FDA at the adult dose for use in children weighing ≥35 kg when used in combination with ATV, and in children weighing ≥40 kg when used in combination with DRV. COBI, coformulated with ATV (as Evotaz),[13] is approved by the FDA at the adult dose for use in children and adolescents weighing ≥35 kg. COBI, coformulated with DRV (as Prezcobix)[14] and as a component of Symtuza,[4] is approved by the FDA at the adult dose in children and adolescents weighing ≥40 kg.

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Ritonavir (RTV, Norvir)

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Formulations
Oral Powder: 100 mg per packet **Oral Solution:** 80 mg/mL. Oral solution contains 43% (v/v) ethanol and approximately 27% (w/v) propylene glycol. **Tablets:** 100 mg **Generic Formulation** • 100-mg tablets **Fixed-Dose Combination (FDC) Solution** • [Kaletra] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol. **FDC Tablets** • [Kaletra] Lopinavir 100 mg/ritonavir 25 mg • [Kaletra] Lopinavir 200 mg/ritonavir 50 mg When using FDC tablets or solution, refer to other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents. For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations	Selected Adverse Events
Ritonavir as a Pharmacokinetic Enhancer • Ritonavir (RTV) is used as a pharmacokinetic (PK) enhancer of other protease inhibitors (PIs). The recommended dose of RTV varies and is specific to the drug combination selected. See other sections of Appendix A: Pediatric Antiretroviral Drug Information for information about the recommended doses of RTV to use with specific PIs. RTV has antiviral activity, but it is not used as an antiviral agent; instead, it is used as a PK enhancer of other PIs. **Formulation Considerations** • The RTV oral solution contains propylene glycol and ethanol. • The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least RTV 100 mg because the oral powder does not contain propylene glycol or ethanol. • RTV oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.	• Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea • Hyperlipidemia, especially hypertriglyceridemia • Hepatitis • Hyperglycemia • Fat maldistribution **Special Instructions** • Administer RTV with food to increase absorption and reduce the likelihood and severity of GI adverse events. • **Do not administer** RTV with cobicistat (COBI) or drugs that contain COBI (e.g., Stribild, Genvoya, Prezcobix, Evotaz). • **Do not refrigerate** RTV oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.

[Kaletra] Lopinavir/Ritonavir	
[Kaletra] Lopinavir/Ritonavir *Infant, Child, Adolescent, and Adult Dose* • See the Lopinavir/Ritonavir section of Appendix A: Pediatric Antiretroviral Drug Information for information.	• RTV oral powder should be mixed with a soft food (e.g., applesauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help mitigate the bitter taste. Administer or discard the mixture within 2 hours of mixing. **To Increase Tolerability of Ritonavir Oral Solution or Oral Powder in Children** • Mix the solution or powder with milk, chocolate milk, ice cream, or vanilla or chocolate pudding. • Before administering RTV, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a nonallergic child peanut butter or hazelnut chocolate spread to coat the mouth.[1] • After administration, give foods with strong tastes (e.g., maple syrup, cheese). • Check a child's food allergy history before making these recommendations. • Counsel caregivers or patients that the bad taste will not be completely masked.
	Metabolism/Elimination
	• Cytochrome P450 (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein. **Ritonavir Dosing in Patients with Hepatic Impairment** • RTV is primarily metabolized by the liver. • No dose adjustment is necessary in patients with mild or moderate hepatic impairment. • No data exist on RTV dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* Ritonavir (RTV) is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P450 (CYP) 3A. Also, RTV is a CYP2D6 inhibitor and a CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein. There is potential for multiple drug interactions with RTV.

- Before RTV is administered, a patient's medication profile should be reviewed carefully for potential interactions with RTV and overlapping toxicities with other drugs.
- RTV and cobicistat **are not interchangeable.** The potential drug interactions for these drugs are different.[2]
- Avoid concomitant use of corticosteroids, including intranasal or inhaled fluticasone or inhaled budesonide. Reduced elimination of steroids can increase steroid effects, leading to adrenal insufficiency.[3,4] Use caution when prescribing RTV with other inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking RTV requires an inhaled or intranasal corticosteroid.[5,6] Iatrogenic Cushing's syndrome and suppression of the hypothalamic-pituitary axis secondary to the drug interaction between RTV and local injection of triamcinolone has occurred.[7,8] See Drug Interactions Between Protease Inhibitors and Other Drugs in the Adult and Adolescent Antiretroviral Guidelines for additional information.

Major Toxicities

- *More common:* Nausea, vomiting, diarrhea, headache, abdominal pain, anorexia, circumoral paresthesia, abnormal lipid levels
- *Less common (more severe):* Exacerbation of chronic liver disease, fat maldistribution
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, pancreatitis. Cases of hepatitis, including life-threatening cases, have been reported. Allergic reactions, including bronchospasm, urticaria, and angioedema. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.[9]

Resistance

Resistance to RTV is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

Pediatric Use

Approval

RTV has been approved by the U.S. Food and Drug Administration for use in the pediatric population.

Effectiveness in Practice

Use of RTV as the sole protease inhibitor (PI) in ARV therapy in children **is not recommended.** In both children and adults, RTV is recommended as a PK enhancer for use with other PIs. RTV is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PI.

Dosing

Dosing regimens for RTV-boosted darunavir and atazanavir and coformulated lopinavir/ritonavir (LPV/r) are available for pediatric patients. For more information about individual PIs, see other sections of Appendix A: Pediatric Antiretroviral Drug Information.

Toxicity

Full-dose RTV has been shown to prolong the PR interval in a study of healthy adults who were given RTV 400 mg twice daily.[9] Potentially life-threatening arrhythmias have been reported in premature infants who were treated with LPV/r; therefore, the use of LPV/r is generally not recommended before a gestational age of 42 weeks (see Lopinavir/Ritonavir).[10,11] Coadministration of RTV with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how coadministering any of these drugs with RTV will affect the PR interval. In addition, RTV should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as patients who have underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

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Fixed-Dose Combinations

Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Brand Name	NRTIs						NNRTIs			INSTIs				PIs			PK Enhancers	
	ABC	3TC	ZDV	FTC	TDF	TAF[a]	DOR	EFV	RPV[b]	BIC[a]	CAB[b]	DTG	EVG[a]	ATV	DRV	LPV[c]	COBI	RTV
NRTI																		
Cimduo		X			X													
Combivir		X	X															
Descovy				X		X												
Epzicom	X	X																
Temixys		X			X													
Truvada				X	X													
NRTI/NNRTI																		
Atripla				X	X			X										
Complera				X	X				X									
Delstrigo		X			X		X											
Odefsey				X		X			X									
Symfi or Symfi Lo		X			X			X										
NRTI/INSTI																		
Biktarvy				X		X				X								
Dovato		X										X						
Triumeq	X	X										X						

Brand Name	NRTIs						NNRTIs			INSTIs				PIs			PK Enhancers	
	ABC	3TC	ZDV	FTC	TDF	TAF[a]	DOR	EFV	RPV[b]	BIC[a]	CAB[b]	DTG	EVG[a]	ATV	DRV	LPV[c]	COBI	RTV
NNRTI/INSTI																		
Juluca									X			X						
Cabenuva									X		X							
NRTI/INSTI/COBI																		
Genvoya				X		X							X				X	
Stribild				X	X								X				X	
NRTI/PI/COBI																		
Symtuza				X		X									X		X	
PI/COBI																		
Evotaz														X			X	
Prezcobix															X		X	
PI/RTV																		
Kaletra																X		X

[a] TAF, BIC, and EVG are only available in FDC tablets. However, TAF 25 mg tablets (Vemlidy) are FDA-approved for treatment of HBV. In select circumstances, TAF might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

[b] CAB and RPV for intramuscular injection are available as a co-packaged product (Cabenuva); oral formulations of CAB and RPV for initial lead in dosing must be prescribed separately, see Cabotegravir and Rilpivirine.

[c] LPV is only available in FDC tablets or solution.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = U.S. Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

General Considerations When Using Fixed-Dose Combination Tablets

- For children weighing ≥14 kg, bictegravir (BIC) is available as the single-tablet, once-daily regimen bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) (Biktarvy).
- For children weighing ≥25 kg, BIC, dolutegravir (DTG), and elvitegravir (EVG) are available as single-tablet, once-daily regimens as BIC/FTC/TAF (Biktarvy), abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) (Triumeq), and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/c/FTC/TAF) (Genvoya).
- BIC and DTG, second-generation integrase strand transfer inhibitors (INSTIs), have a higher barrier to resistance than the first-generation INSTI EVG.
- EVG/c/FTC/TAF (Genvoya) has more drug–drug interactions than ABC/DTG/3TC (Triumeq) or BIC/FTC/TAF (Biktarvy).
- Abacavir (ABC) or tenofovir alafenamide (TAF) in combination with lamivudine (3TC) or emtricitabine (FTC) are favored over zidovudine/lamivudine (ZDV/3TC) because of the lower risk of nucleoside reverse transcriptase inhibitor (NRTI)–associated mitochondrial toxicity.
- Tenofovir disoproxil fumarate (TDF) is more potent than ABC at high viral loads when used in regimens that do not contain an INSTI.
- TAF is favored over TDF because of the lower risk of TDF-associated bone and renal toxicity.
- TDF is not recommended for children with sexual maturity ratings (SMRs) of 1 to 3 because of TDF-associated bone toxicity. For children weighing ≥14 kg to <25 kg who can swallow pills, (FTC/TAF) (Descovy) offers a once-daily alternative to twice-daily ZDV plus 3TC or ABC plus 3TC. For children weighing ≤35 kg, FTC/TAF (Descovy) can be used in combination with an INSTI or NNRTI, but not with a protease inhibitor; this restriction does not apply to regimens containing ZDV or ABC.
- The fixed-dose combination (FDC) tablet DOR/3TC/TDF is approved by the U.S. Food and Drug Administration (FDA) for children and adolescents weighing ≥35 kg who are antiretroviral (ARV) naive or virologically suppressed on a stable ARV regimen (see the Doravirine section).
- Rilpivirine (RPV) has low potency at high viral loads, a low barrier to resistance, and requires a high-fat meal for optimal absorption, so EFV or an INSTI are favored over RPV.

- The possibility of planned and unplanned pregnancy should be considered when selecting an antiretroviral therapy (ART) regimen for an adolescent. When discussing ART options with adolescents of childbearing potential and their caregivers, it is important to consider the benefits and risks of all ARV drugs and to provide the information and counseling needed to support informed decision-making (see Table 5. Situation-Specific Recommendations for Use of Antiretroviral Drugs in Pregnant People and Nonpregnant People Who Are Trying to Conceive and Appendix C: Antiretroviral Counseling Guide for Health Care Providers).
- For images of most of the FDC tablets listed in this table, see the Antiretroviral Medications section of the National HIV Curriculum. In addition, a resource from the United Kingdom illustrates the relative sizes of FDC tablets and individual ARV drugs (see the ARV Chart). Although most of the drugs listed in that chart are the same as those in the United States, a few of the brand names are not the same as those listed in this Appendix.
- FDC tablets and individual ARV drugs also can be looked up by drug name (brand name and generic) at DailyMed. Size is listed under the Ingredients and Appearance section.

Integrase Strand Transfer Inhibitor Fixed-Dose Combination Dosing for Children and Adolescents

Bictegravir

- BIC/FTC/TAF (Biktarvy) is approved for pediatric use by the FDA with two dosage strengths: one for use in children weighing 14 to <25 kg and another for children and adolescents weighing ≥25 kg and adults.

Dolutegravir

- The recommended dose of DTG for children and adolescents weighing ≥20 kg is DTG 50 mg using film-coated tablets or DTG 30 mg using dispersible tablets. **DTG film-coated tablets and DTG dispersible tablets are not bioequivalent and are not interchangeable on a milligram-per-milligram basis,** refer to Dolutegravir for dosing information**.**
  - Children weighing ≥20 kg to <25 kg who can swallow pills can be treated with DTG 50-mg film-coated tablets plus FTC/TAF (Descovy) 120 mg FTC/15 mg TAF taken orally once daily.
  - For children weighing ≥25 kg who can swallow pills, DTG 50 mg can be given as Triumeq (ABC/DTG/3TC) in one large pill taken once daily or as FTC/TAF (Descovy) 200 mg FTC/25 mg TAF plus DTG 50-mg film-coated tablets, which requires two small pills taken once daily. The FDA has approved ABC/DTG/3TC (Triumeq) for pediatric patients weighing ≥40 kg, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends this FDC for use in patients weighing ≥ 25 kg.

Elvitegravir

- EVG/c/FTC/TAF (Genvoya) is approved by the FDA for children and adolescents weighing ≥25 kg.

FDC by Class Brand name and generic[a] products, when available	**FDC Components**	**Minimum Body Weight or Weight Range (kg) or Age[b]**	**Pill Size (mm × mm) or Largest Dimension (mm)**	**Food Requirements**
NRTI				
Cimduo	3TC 300 mg/TDF 300 mg	35 kg	19	Take with or without food.
Combivir and Generic 3TC/ZDV	3TC 150 mg/ZDV 300 mg (scored tablet)	30 kg	18 × 7	Take with or without food.
Descovy	FTC 120 mg/TAF 15 mg	**With an INSTI or NNRTI** • 14 to < 25 kg	N/A	Take with or without food.
	FTC 200 mg/TAF 25 mg	**With an INSTI or NNRTI** • 25 kg **With a Boosted PI** • 35 kg	12.5 × 6.4	Take with or without food.
Epzicom and Generic ABC/3TC	ABC 600 mg/3TC 300 mg	25 kg	21 × 9	Take with or without food.
Temixys	3TC 300 mg/TDF 300 mg	35 kg	N/A	Take with or without food.
Truvada	FTC 100 mg/TDF 150 mg	17 to <22 kg	14	Take with or without food.
	FTC 133 mg/TDF 200 mg	22 to <28 kg	16	Take with or without food.
	FTC 167 mg/TDF 250 mg	28 to <35 kg	18	Take with or without food.
	FTC 200 mg/TDF 300 mg	35 kg	19 × 8.5	Take with or without food.
NRTI/NNRTI				
Atripla	EFV 600 mg/FTC 200 mg/TDF 300 mg	40 kg	20	Take on an empty stomach.

FDC by Class Brand name and generic[a] products, when available	**FDC Components**	**Minimum Body Weight or Weight Range (kg) or Age[b]**	**Pill Size (mm × mm) or Largest Dimension (mm)**	**Food Requirements**
Complera	FTC 200 mg/RPV 25 mg/TDF 300 mg	35 kg and aged ≥12 years	19	Take on an empty stomach.
Delstrigo	DOR 100 mg/3TC 300 mg/TDF 300 mg	35 kg	19	Take with or without food.
Odefsey	FTC 200 mg/RPV 25 mg/TAF 25 mg	35 kg and aged ≥12 years	15	Take with a meal.
Symfi	EFV 600 mg/3TC 300 mg/TDF 300 mg (scored tablet)	40 kg	23	Take on an empty stomach.
Symfi Lo	EFV 400 mg/3TC 300 mg/TDF 300 mg	35 kg[c]	21	Take on an empty stomach.
NRTI/INSTI				
Biktarvy	BIC 30 mg/FTC 120 mg/TAF 15 mg	14 to <25 kg	N/A	Take with or without food.
	BIC 50 mg/FTC 200 mg/TAF 25 mg	25 kg	15 × 8	Take with or without food.
Dovato	DTG 50 mg/3TC 300 mg	Adults[d]	19	Take with or without food.
Triumeq	ABC 600 mg/DTG 50 mg/3TC 300 mg	40 kg (FDA) 25 kg (the Panel)[e]	22 × 11	Take with or without food.
NNRTI/INSTI				
Cabenuva[f]	Cabenuva 400 mg/600 mg kit contains CAB 400 mg/2 mL vial and RPV 600 mg/2 mL vial	Adults	N/A	See Cabotegravir for instructions about dosing and administration.
	Cabenuva 600 mg/900 mg kit contains CAB 600 mg/3 mL vial and RPV 900 mg/3 mL vial	Adults	N/A	See Cabotegravir for instructions about dosing and administration.
Juluca	DTG 50 mg/RPV 25 mg	Adults[d]	14	Take with a meal.
NRTI/INSTI/COBI				
Genvoya	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	25 kg	19 × 8.5	Take with food.
Stribild	EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg	35 kg and SMR 4 or 5[g]	20	Take with food.
NRTI/PI/COBI				
Symtuza	DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	40 kg	22	Take with food.
PI/COBI				
Evotaz	ATV 300 mg/COBI 150 mg	35 kg	19	Take with food.
Prezcobix	DRV 800 mg/COBI 150 mg	40 kg	23	Take with food.

FDC by Class Brand name and generic[a] products, when available	**FDC Components**	**Minimum Body Weight or Weight Range (kg) or Age[b]**	**Pill Size (mm × mm) or Largest Dimension (mm)**	**Food Requirements**
PI/RTV				
Kaletra	**LPV/r Oral Solution** • LPV 80 mg/mL and RTV 20 mg/mL **Tablets** • LPV 200 mg/RTV 50 mg • LPV 100 mg/RTV 25 mg	**Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days** • No minimum weight	19	Take with or without food.

[a] Sizes or largest dimensions of generic drugs are not listed because they may vary by manufacturer; this information is available by looking up one of the drug components using DailyMed.

[b] Minimum body weight and age are those recommended by the FDA, unless otherwise noted.

[c] Because of pharmacokinetic concerns, the Panel recommends caution when using Symfi Lo in children and adolescents who have SMRs of 1 to 3 and weigh ≥40 kg (see the Efavirenz section).

[d] The Panel does not currently recommend using dolutegravir/lamivudine (DTG/3TC) (Dovato) or dolutegravir/rilpivirine (DTG/RPV) (Juluca) as a two-drug complete regimen in adolescents and children. These FDC tablets could be used as part of a three-drug regimen in children who meet the minimum body weight requirements for each component drug.

[e] The Panel recommends using DTG 50 mg for children and adolescents weighing ≥20 kg based on available data; however, the doses of ABC and 3TC in Triumeq are too high for children weighing <25 kg (see the Dolutegravir section).

[f] Long-acting cabotegravir (CAB) and RPV for intramuscular injection are available as a co-packaged product (Cabenuva); oral formulations of CAB and RPV for initial lead-in dosing must be prescribed separately (see the Cabotegravir and Rilpivirine sections).

[g] Although Stribild is approved by the FDA for use in children and adolescents weighing ≥35 kg and age ≥12 years, the Panel **does not recommend** its use in children with SMRs 1 to 3 given the availability of other INSTI-containing FDCs.

Key: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = U.S. Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; kg = kilogram; LPV = lopinavir; LPV/r = lopinavir/ritonavir; mg = milligram; mL = milliliter; mm = millimeter; N/A = information not available or not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Archived Drugs

Overview

The Archived Drugs section of Appendix A: Pediatric Antiretroviral Drug Information provides access to the last updated versions of drug sections that are no longer being reviewed by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel). Archived Drugs includes older antiretroviral drugs that the Panel does not recommend for use in children because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data.

Didanosine

Enfuvirtide

Fosamprenavir

Indinavir

Nelfinavir

Saquinavir

Stavudine

Tipranavir

Didanosine (ddI, Videx) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Pediatric Oral Solution: 10 mg/mL

Enteric-Coated (EC) Delayed-Release Capsules (EC Beadlets): 125 mg, 200 mg, 250 mg, and 400 mg

Generic Formulations

Delayed-Release Capsules: 125 mg, 200 mg, 250 mg, and 400 mg

Dosing Recommendations

Note: Didanosine **is no longer recommended** by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV for use in children due to higher rates of adverse effects than other NRTIs.

Neonate/Infant Dose (Aged 2 Weeks to <3 Months):

- 50 mg/m² of body surface area every 12 hours. See dosing section below for justification of this dose.

Infant Dose (Aged ≥3 Months to 8 Months):

- 100 mg/m² body surface area every 12 hours

Pediatric Dose of Oral Solution (Age >8 Months):

- 120 mg/m² body surface area every 12 hours
- Dose range: 90–150 mg/m² body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naive children ages 3 years to 21 years, 240 mg/m² body surface area once daily (oral solution or capsules) has resulted in viral suppression.

Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Weighing ≥20 kg)

Body Weight	Dose
20 kg to <25 kg	200 mg once daily
25 kg to <60 kg	250 mg once daily
≥60 kg	400 mg once daily

Adolescent and Adult Dose

Body Weight	Dose
<60 kg	250 mg once daily
≥60 kg	400 mg once daily

Selected Adverse Events

- Peripheral neuropathy
- Diarrhea, abdominal pain, nausea, and vomiting
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported (the risk is increased when didanosine is used in combination with stavudine).
- Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with tenofovir disoproxil fumarate or stavudine)
- Non-cirrhotic portal hypertension
- Retinal changes, optic neuritis
- Insulin resistance/diabetes mellitus

Special Instructions

- Administer didanosine on an empty stomach (30 minutes before or 2 hours after a meal). To improve adherence, some practitioners administer didanosine without regard to timing of meals (see text below).
- Didanosine powder for oral solution contains antacids that may interfere with the absorption of other medications, including protease inhibitors (PIs). See individual PI for instructions on timing of administration.
- Shake didanosine oral solution well before use. Keep refrigerated; solution is stable for 30 days.

Metabolism/Elimination

- Renal excretion 50%

Pediatric and Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate:

- This combination should be avoided because of enhanced didanosine toxicity, reports of immunologic nonresponse, high rates of early virologic failure, and rapid selection of resistance mutations (see the Adult and Adolescent Guidelines).
- Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance.

Drug Interactions (see also the Adult and Adolescents Guideline and HIV Drug Interaction Checker)

- *Absorption:* Antacids in didanosine oral solution can decrease the absorption of a number of medications if given at the same time. Avoid giving other medications concurrently with didanosine oral solution.
- *Mechanism unknown:* Didanosine serum concentrations are increased when didanosine is co-administered with tenofovir disoproxil fumarate (TDF). This combination should be avoided.
- *Renal elimination:* Drugs that decrease renal function can decrease didanosine clearance.
- *Overlapping toxicities:* The combination of stavudine with didanosine may result in enhanced toxicity. This combination should be avoided (see the Major Toxicities section below).

Major Toxicities

- *More common:* Diarrhea, abdominal pain, nausea, and vomiting.
- *Less common (more severe):* Peripheral neuropathy, electrolyte abnormalities, and hyperuricemia. Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported, and are more common when didanosine is used in combination with stavudine. Pancreatitis (less common in children than in adults, more common when didanosine is used in combination with TDF or stavudine) can occur. Increased liver enzymes, retinal depigmentation, and optic neuritis have been reported. Decreases in CD4 T lymphocyte counts have been reported when didanosine is used in combination with TDF.
- *Rare:* Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use.[1]
- *Possible risk of cancer after in-utero exposure:* In a study of 15,163 children without HIV infection who were exposed to at least one nucleoside reverse transcriptase inhibitor (NRTI) *in utero*, 21 cancers were identified. Didanosine accounted for only 10% of prescriptions but was associated with one-third of identified cancers, and, in multivariate analysis, didanosine was associated with a 5.5-fold (95% CI, 2.1–14.4) increased risk of cancer with first-trimester exposure.[2] Pregnant adolescents or sexually active female adolescents on didanosine should be cautioned about this risk.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Although didanosine is a Food and Drug Administration (FDA)-approved NRTI for use in children as part of antiretroviral therapy, **it is not recommended** for use in children due to its significant toxicity and the availability of safer agents.

Dosing

Standard Dose in Children Aged >8 Months

The standard dose of didanosine oral solution in children aged >8 months is 120 mg/m^2 of body surface area twice daily.[3,4] Doses higher than 180 mg/m^2 of body surface area twice daily are associated with increased toxicity.[5]

Special Considerations for Children Aged 2 Weeks to <8 Months

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m^2 of body surface area per dose twice daily. However, because pharmacokinetic (PK) differences in younger infants (aged 2 weeks–3 months) compared with older children raise concerns for increased toxicity in this younger age group, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends a dose of 50 mg/m^2 of body surface area twice daily for infants aged 2 weeks to 3 months, with an increase to 100 mg/m^2 of body surface area per dose twice daily at 3 months, and finally increasing to 120 mg/m^2 of body surface area per dose twice daily at age 8 months (as discussed above).

Frequency of Administration (Once Daily or Twice Daily)

In those aged >3 years, a once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing of 240 mg/m^2 of body surface area.[6]

Food Restrictions

Although the prescribing information recommends taking didanosine on an empty stomach, this is impractical for infants who must be fed frequently, and it may decrease medication adherence by increasing regimen complexity. A comparison showed that systemic exposure measured by area under the curve was similar whether didanosine oral solution was given to children with or without food; absorption of didanosine administered with food was slower and elimination more prolonged.[7] To improve adherence, some practitioners administer didanosine without regard to timing of meals. Studies in adults suggest that didanosine can be given without regard to food.[8,9] A European study dosed didanosine oral solution as part of a four-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction. The study showed good virologic outcome with up to 96 weeks of follow-up.[10]

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Enfuvirtide (T-20, Fuzeon) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Lyophilized Powder for Injection:

- 108-mg vial of enfuvirtide. Reconstitution with 1.1 mL sterile water will deliver 90 mg/mL.

Convenience Kit:

- 60 single-use vials of enfuvirtide (108-mg vial reconstituted as 90 mg/mL), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes.

Dosing Recommendations

Pediatric and Adolescent Dose (Aged 6–16 Years)

Children Aged <6 Years:

- Not approved for use in children aged <6 years

Children Aged ≥6 Years:

- 2 mg/kg (maximum dose 90 mg [1 mL]) twice daily injected subcutaneously (SQ) into the upper arm, anterior thigh, or abdomen

Adolescent (Aged >16 Years) and Adult Dose:

- 90 mg (1 mL) twice daily injected SQ into the upper arm, anterior thigh, or abdomen

Selected Adverse Events

- Local injection site reactions (e.g., pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in up to 98% of patients.
- Increased rate of bacterial pneumonia (unclear association).
- Hypersensitivity reaction (HSR)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

Special Instructions

- Carefully instruct patient or caregiver in proper technique for drug reconstitution and administration of SQ injections. Enfuvirtide injection instructions are provided with convenience kits.
- Allow reconstituted vial to stand until the powder goes completely into solution, which could take up to 45 minutes. Do not shake.
- Once reconstituted, inject enfuvirtide immediately or keep refrigerated in the original vial until use. Reconstituted enfuvirtide must be used within 24 hours.
- Enfuvirtide must be given SQ; severity of reactions increases if given intramuscularly.
- Give each injection at a site different from the preceding injection site; do not inject into moles, scar tissue, bruises, or the navel. Both the patient/caregiver and health care provider should carefully monitor for signs and symptoms of local infection or cellulitis.
- To minimize local reactions, apply ice or heat after injection or gently massage injection

site to better disperse the dose. There are reports of injection-associated neuralgia and paresthesia when alternative delivery systems, such as needle-free injection devices, are used.

- Advise patients/caregivers of the possibility of a HSR; instruct them to discontinue treatment and seek immediate medical attention if a patient develops signs and symptoms consistent with a HSR.

Metabolism/Elimination

- Catabolism to constituent amino acids.

Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- There are no known significant drug interactions with enfuvirtide.

Major Toxicities

- *More common:* Almost all patients (87% to 98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days but was >7 days in 24% of patients.
- *Less common (more severe):* Increased rate of bacterial pneumonia (unclear association).[1] Pediatric studies have lacked the statistical power to answer questions concerning enfuvirtide use and increased risk of pneumonia.
- *Rare:* Hypersensitivity reactions (HSRs) (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing HSRs should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with HSRs.
- *Pediatric specific:* Local site cellulitis requiring antimicrobial therapy (up to 11% in certain subgroups of patients in pediatric studies).[2]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Resistance testing must be ordered specifically for fusion inhibitors, as it is not performed on routine genotypic or phenotypic assays.

Pediatric Use

Approval

Although enfuvirtide is Food and Drug Administration (FDA)-approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high rate of injection site reactions. Use in deep salvage regimens[3] has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).

Pharmacokinetics

A single-dose pharmacokinetic evaluation study of enfuvirtide, given SQ to 14 children with HIV aged 4 years to 12 years (PACTG 1005), identified that enfuvirtide 60 mg/m^2 of body surface area per dose resulted in a target trough concentration that approximated the equivalent of a 90-mg dose delivered SQ to an adult (1000 mg/mL).[4] In a second pediatric study of 25 children aged 5 years to 16 years, a 2-mg/kg dose (maximum 90 mg) of enfuvirtide given twice daily yielded drug concentrations similar to 60 mg/m^2 of body surface area dose independent of age group, body weight, body surface area, and sexual maturation.[5] The FDA-recommended dose of enfuvirtide for children aged 6 years to 16 years is 2 mg/kg (maximum 90 mg) administered SQ twice daily. Further data are needed for dosing in children aged <6 years.

Efficacy

The safety and antiretroviral (ARV) activity of twice-daily SQ enfuvirtide administration at 60 mg/m^2 per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children aged 4 to 12 years who had failed to achieve viral suppression on multiple prior ARV regimens (PACTG 1005). At 24 weeks 71% of the children had a $>1.0_{log}$ reduction in viral load; 43% and 21% had HIV RNA levels suppressed to <400 copies/mL and <50 copies/mL, respectively. However, only 36% of children maintained virologic suppression ($>1.0_{log}$ decrease in HIV RNA) at Week 96. Most children had local injection site reactions.[6] Significant improvements in CD4 T lymphocyte (CD4) cell percentages and height *z* scores were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase 1/2 study of enfuvirtide (2.0 mg/kg SQ, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children aged 3 to 16 years for 48 weeks. Only 64% of the children completed 48 weeks of therapy. The median decrease in HIV RNA was -1.17 $\log_{10}$ copies/mL (n = 32) and increase in CD4 cell count was 106 cells/mm^3 (n = 25). At Week 8, treatment responses as measured by several plasma HIV RNA parameters were superior in younger children (aged <11 years) compared with adolescents. Median increases in CD4 cell count were 257 cells/mm^3 in children and 84 cells/mm^3 in adolescents. Local skin reactions were common in all age groups (87% of study participants). The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen.[2]

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Fosamprenavir (FPV, Lexiva) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 700 mg

Oral Suspension: 50 mg/mL

Dosing Recommendations

Pediatric Dose (Aged >6 Months to 18 Years):

- Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but not recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants ≥4 weeks and for treatment-experienced infants ≥6 months; however, the Panel does not recommend use in infants aged <6 months because of similarly low exposures (see text below). If used in infants as young as 4 weeks, it should only be administered to infants born at 38 weeks' gestation or greater.

Note: Once-daily dosing **is not recommended** for any pediatric patient.

Pediatric Dose (Aged ≥6 Months to 18 Years):

Twice-Daily Dose Regimens by Weight for Pediatric Patients ≥6 Months Using Fosamprenavir Oral Suspension with Ritonavirr

Weight	Dose (Both Drugs Twice Daily[a] with Food)
<11 kg	Fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose
11 kg to <15 kg	Fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose
15 kg to <20 kg	Fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose
≥20 kg	Fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose

[a] Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (fosamprenavir has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- Fosamprenavir tablets with ritonavir should be taken with food. Children should take the suspension with food.
- Patients taking antacids should take fosamprenavir at least 1 hour before or after antacid use.
- Fosamprenavir contains a sulfonamide moiety. The potential for cross sensitivity between fosamprenavir and other drugs in the sulfonamide class is unknown. Fosamprenavir should be used with caution in patients with sulfonamide allergy.
- Shake oral suspension well before use. Refrigeration is not required.

Metabolism/Elimination

- The prodrug fosamprenavir is rapidly and almost completely hydrolyzed to amprenavir by cellular phosphatases in the gut as it is absorbed.
- Amprenavir is a cytochrome P (CYP) 450 3A4 inhibitor, inducer, and substrate.

Note: When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing ≥39 kg. Ritonavir tablets can be used in patients weighing ≥33 kg.

Adolescent and Adult Dose:

- Dosing regimen depends on whether the patient is ARV-naive or ARV-experienced.

ARV-Naive Patients

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily
- Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily

Protease-Inhibitor-Experienced Patients:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily

Note: Once-daily administration of fosamprenavir plus ritonavir **is not recommended**.

Fosamprenavir Dosing in Patients with Hepatic Impairment:

- Specific dose adjustments are recommended for adults with mild, moderate, and severe hepatic impairment. However, there are no data to support dosing recommendations for pediatric patients with hepatic impairment. Please refer to the package insert.

Fosamprenavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required in patients with renal impairment.

Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- Fosamprenavir may interact with a number of other drugs, and using ritonavir as a boosting agent increases the potential for drug interactions. Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with fosamprenavir.

Major Toxicities

- *More common:* Vomiting, nausea, diarrhea, perioral paresthesia, headache, rash, and lipid abnormalities.
- *Less common (more severe):* Life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients. Fat maldistribution, neutropenia, and elevated serum creatinine kinase levels.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, hemolytic anemia, elevation in serum transaminases, angioedema, and nephrolithiasis.
- *Pediatric-specific:* Vomiting was more frequent in children than in adults during clinical trials of fosamprenavir with ritonavir (20% to 36% vs. 10%, respectively) and in trials of fosamprenavir without ritonavir (60% vs. 16%, respectively). Neutropenia was also more common in children across all the trials (15% vs. 3%, respectively).[1]

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the

Panel) recommends use only in children aged ≥6 months. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naive children aged 2 to 5 years, the Panel does not recommend unboosted fosamprenavir for this—or any other—age group because of low exposures and also because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.[2]

Efficacy and Pharmacokinetics

Dosing recommendations for fosamprenavir are based on three pediatric studies that enrolled more than 200 children aged 4 weeks to 18 years. In two, open-label trials in both treatment-experienced and treatment-naive children aged 2 to 18 years,[3,4] fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of fosamprenavir/ritonavir in children; therefore, once-daily dosing is not recommended for pediatric patients.

Pharmacokinetics in Infants

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naive infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months.[1,5] Exposures in those aged <6 months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir (see table below). Given these low exposures, limited data, large dosing volumes, unpleasant taste, and the availability of alternatives for infants and young children, the Panel does not recommend fosamprenavir use in infants aged <6 months.

Table A. Fosamprenavir Dose and Amprenavir Exposure by Age Group

Population	Dose	$AUC_{0\text{-}24h}$ (mcg*hr/mL) Except Where Noted	C_{min} (mcg/mL)
Infants Aged <6 Months	FPV 45 mg/kg plus RTV 10 mg/kg twice daily	26.6[a]	0.86
Children Aged 2 Years to <6 Years	FPV 30 mg/kg twice daily (no RTV)	22.3[a]	0.513
Children Weighing <11 kg	FPV 45 mg/kg plus RTV 7 mg/kg twice daily	57.3	1.65
Children Weighing 15 kg to <20 kg	FPV 23 mg/kg FPV plus RTV 3 mg/kg twice daily	121.0	3.56
Children Weighing ≥20 kg	FPV 18 mg/kg plus RTV 3 mg/kg twice daily (maximum 700/100 mg)	72.3–97.9	1.98–2.54
Adults	FPV 1400 mg twice daily (no RTV)	33	0.35
Adults	FPV 1400 mg plus RTV 100–200 mg RTV once daily	66.4–69.4	0.86–1.45
Adults	FPV 700 mg plus RTV 100 mg twice daily	79.2	2.12

[a] $AUC_{0\text{-}12}$ (mcg*hr/mL)

Key to Acronyms: $AUC_{0\text{-}24h}$ = area under the curve for 24 hours post-dose; C_{min} = minimum plasma concentration; FPV = fosamprenavir; RTV = ritonavir

Note: Dose for those weighing 11 kg to <15 kg is based on population pharmacokinetic studies; therefore, AUC and C_{min} are not available.

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Indinavir (IDV, Crixivan) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Capsules: 100 mg, 200 mg, and 400 mg

Dosing Recommendations

Neonate and Infant Dose:

- Not approved for use in neonates/infants
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus)

Pediatric Dose:

- Not approved for use in children
- A range of indinavir doses (234–500 mg/m^2 body surface area) boosted with low-dose ritonavir has been studied in children (see text below).

Adolescent and Adult Dose:

- 800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **does not recommend** the use of indinavir in adolescents.

Selected Adverse Events

- Nephrolithiasis
- Gastrointestinal intolerance, nausea
- Hepatitis
- Indirect hyperbilirubinemia
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

Special Instructions

- When indinavir is given in combination with ritonavir, meal restrictions are not necessary.
- Adequate hydration is required to minimize risk of nephrolithiasis (≥48 oz of fluid daily in adult patients).
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate

Indinavir Dosing in Patients with Hepatic Impairment:

- Dose should be decreased in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

Drug Interactions (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions with indinavir.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

Major Toxicities

- *More common:* Nephrolithiasis/urolithiasis with indinavir crystal deposit is reported more frequently in children (29%) than in adults (12.4%).[1] Interstitial nephritis and urothelial inflammation has been commonly reported in adults.[2] Nausea, abdominal pain, headache, metallic taste, dizziness, asymptomatic hyperbilirubinemia (10%), lipid abnormalities, pruritus, and rash.
- *Less common (more severe):* Fat maldistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, acute hemolytic anemia, and hepatitis (life-threatening in rare cases).

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Indinavir has not been approved by the Food and Drug Administration for use in the pediatric population. Although indinavir was one of the first protease inhibitors to be studied in children, its use in pediatrics has never been common and is currently very rare.[3] Indinavir **is not recommended** by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV for use in children and adolescents because of its unfavorable toxicity profile, limited efficacy data, and uncertain pharmacokinetics.

Efficacy and Pharmacokinetics

Both unboosted and ritonavir-boosted indinavir have been studied in children with HIV. In children, an unboosted indinavir dose of 500 to 600 mg/m^2 body surface area given every 8 hours results in peak blood concentrations and area under the curve that are slightly higher than those in adults, but trough concentrations are considerably lower. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults.[4-7] Studies that investigated a range of indinavir/ritonavir doses in small groups of children have shown that indinavir 500 mg/m^2 body surface area plus ritonavir 100 mg/m^2 body surface area twice daily is probably too high,[8] that indinavir 234 to 250 mg/m^2 body surface area plus low-dose ritonavir twice daily is too low,[9,10] and that indinavir 400 mg/m^2 body surface area plus ritonavir 100 to 125 mg/m^2 body surface area twice daily results in exposures approximating those seen with indinavir 800 mg plus ritonavir 100 mg twice daily in adults, albeit with considerable inter-individual variability and high rates of toxicity.[10-12]

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Nelfinavir (NFV, Viracept) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 250 mg and 625 mg

Dosing Recommendations

Note: The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **no longer recommends** nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.

Neonate and Infant Dose:

- Nelfinavir should not be used for treatment in children aged <2 years.

Pediatric Dose (Aged ≥2 Years):

- 45–55 mg/kg twice daily

Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily

Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Serum transaminase elevations

Special Instructions

- Administer nelfinavir with meal or light snack.
- If co-administered with didanosine, administer nelfinavir 2 hours before or 1 hour after didanosine.
- Patients unable to swallow nelfinavir tablets can dissolve the tablets in a small amount of water. Once tablets are dissolved, mix the cloudy mixture well and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure that the entire dose is consumed. Tablets can also be crushed and administered with pudding or other nonacidic foods.

Metabolism/Elimination

- Cytochrome P (CYP) 2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

Drug Interactions (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Cytochrome P (CYP) 2C19 and 3A4 substrate and CYP3A4 inhibitor. Ritonavir boosting does not significantly increase nelfinavir concentrations, and co-administration of nelfinavir with ritonavir is not recommended.
- There is potential for multiple drug interactions with nelfinavir. Before administering nelfinavir, carefully review a patient’s medication profile for potential drug interactions.

Major Toxicities

- *More common:* Diarrhea (most common), asthenia, abdominal pain, rash, and lipid abnormalities.
- *Less common (more severe):* Fat redistribution and exacerbation of chronic liver disease.

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, and elevations in transaminases.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Nelfinavir is approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years. Given the higher variability of nelfinavir plasma concentrations in infants and younger children,[1,2] nelfinavir is not approved for children aged <2 years. Despite being FDA-approved for pediatric use, nelfinavir **is not recommended** for use in children and adolescents by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, due to its limited efficacy and uncertain pharmacokinetics (PK).

Efficacy in Pediatric Clinical Trials

Nelfinavir used in combination with other antiretroviral (ARV) drugs has been extensively studied in children with HIV infection.[3-10] In randomized trials of children aged 2 to 13 years receiving nelfinavir as part of triple combination therapy, the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26% to 69%. The antiviral response to nelfinavir is significantly less in children aged <2 years than in older children.[8,10,11] In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior treatment history, the number of drugs included in the combination regimen, and the dose of nelfinavir used.

Pharmacokinetics: Exposure-Response Relationships

Nelfinavir's relatively poor ability to control plasma viremia in infants and children in clinical trials may be related to its lower potency when compared with other ARV drugs, as well as highly variable drug exposure, metabolism, and poor palatability.[12-14] The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.[3,15]

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increases by up to five-fold) and decreases PK variability when compared to the fasted state. Nelfinavir plasma exposure may be even more unpredictable in pediatric patients than in adults due to the increased clearance of nelfinavir observed in children and difficulties in taking nelfinavir with sufficient food to improve bioavailability.

Nelfinavir is metabolized by multiple CYP450 enzymes, including CYP3A4 and CYP2C19. The variability of drug exposure at any given dose is much higher for children than for adults,[16] which has been attributed—at least in part—to differences in the diets of children and adults. Two population PK studies of nelfinavir and its active metabolite, M8, describe the large intersubject variability observed in children.[17,18] Furthermore, CYP2C19 genotype has been shown to affect nelfinavir PK and the virologic responses in children with HIV.[12]

Several studies have demonstrated a correlation between nelfinavir trough concentrations and virologic response. In both children and adults, an increased risk of virologic failure was associated with low nelfinavir drug exposure, particularly with a nelfinavir minimum plasma concentration (C_{min}) <1.0 mcg/mL.[19-21]

In a study of 32 children treated with a high dose of nelfinavir (a two-fold increase of the recommended dose), 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had HIV RNA concentrations <50 copies/mL at Week 48, compared with only 29% of those with morning trough <0.8 mcg/mL.[22] Children in the group with C_{trough} <0.8 mcg/mL were younger than the children in the group with C_{trough} >0.8 mcg/mL (median ages in these groups were 3.8 years and 8.3 years, respectively).[22] Therapeutic drug monitoring of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, has been shown to improve virologic response in adults and children.[18,19,23,24] Pediatric and adolescent patients may require doses higher than those recommended in adults to achieve higher plasma nelfinavir exposure.

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Saquinavir (SQV, Invirase) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Capsules: 200 mg

Tablets: 500 mg

Dosing Recommendations

Pediatric Dose:

- Not approved for use in infants, children, and adolescents aged <16 years.

Adolescent and Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg twice daily

Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (Torsades de Pointes)

Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram is recommended; saquinavir is **contraindicated** in patients with a prolonged QT interval.

Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor
- 90% metabolized in the liver
- Use saquinavir with caution in patients who have hepatic impairment; no dose adjustment recommended.

Drug Interactions (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- Saquinavir is both a substrate and inhibitor of the cytochrome P 450 3A4 (CYP3A4) system. Potential exists for multiple drug interactions. Saquinavir **should not be coadministered** with drugs that are highly dependent on CYP3A clearance, especially in cases where elevated plasma concentrations of the coadministered drug can cause serious or life-threatening events.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash, and lipid abnormalities.

- *Less common (more severe):* Exacerbation of chronic liver disease, lipodystrophy.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, pancreatitis, and elevation in serum transaminases. Saquinavir administered with ritonavir can lead to prolonged QT and/or PR intervals with potential for heart block and ventricular tachycardia (Torsades de Pointes).

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Saquinavir is not approved for use in children or adolescents aged <16 years.[1]

Efficacy

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors and other protease inhibitors in children with HIV.[2-9] Saquinavir/ritonavir (SQV/r) and a dual-protease inhibitor saquinavir/lopinavir/ritonavir regimen were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications; these regimens **are no longer recommended**.

Pharmacokinetics

Pharmacokinetic (PK) data from children who received SQV/r showed prohibitively low exposure in children younger than 2 years.[10] In children aged ≥2 years, a dose of saquinavir 50 mg/kg twice daily in combination with ritonavir and lopinavir/ritonavir resulted in steady-state plasma trough concentrations (C_{trough}) similar to those seen adults.[9,11] No clinical trials have collected data on the efficacy of saquinavir doses <50 mg/kg in children.

Toxicity

In healthy adult volunteers, SQV/r dose and exposure were associated with increases in both QT and PR intervals.[1,12] Rare cases of Torsades de Pointes and complete heart block have been reported in postmarketing surveillance. SQV/r **is not recommended** for adolescent and adult patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds, refractory hypokalemia or hypomagnesemia, complete atrioventricular block without implanted pacemakers, at risk of complete atrioventricular block, or the use of other drugs that prolong QT interval. An electrocardiogram (EKG) is recommended before initiation of therapy with saquinavir and repeat EKGs should be considered during therapy.

Steady-state saquinavir exposures observed in one pediatric trial (NV20911) were substantially higher than those seen in historical data from adults with QT and PR prolongation.[1,12] Although no EKG abnormalities have been reported among the small number of subjects in pediatric trials, pediatric PK/pharmacodynamics modeling suggests that reducing the saquinavir dose in order to minimize the risk of QT prolongation would decrease saquinavir efficacy in children. Pediatric saquinavir dose recommendations that were both reliably effective and below the thresholds of concern for QT and PR prolongation were not determined.

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Stavudine (d4T, Zerit) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, and 40 mg

Generic Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, and 40 mg

Dosing Recommendations

Note: Stavudine **is no longer recommended** for use in children by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, because it causes higher rates of adverse effects than other nucleoside reverse transcriptase inhibitors (NRTIs).

Pediatric (Aged ≥14 Days and Weighing <30 kg) Dose:

- 1 mg/kg per dose twice daily

Adolescent (Weighing ≥30 kg) and Adult Dose:

- 30 mg per dose twice daily

Selected Adverse Events

- Associated with a higher risk of mitochondrial toxicity than other NRTI drugs
- Peripheral neuropathy is dose-related and occurs more frequently in patients who have advanced HIV disease or a prior history of peripheral neuropathy, and in patients receiving other drugs associated with neuropathy.
- Facial/peripheral lipoatrophy
- Pancreatitis
- Lactic acidosis/severe hepatomegaly with hepatic steatosis (higher incidence than with other NRTIs). The risk increases when stavudine is used in combination with didanosine.
- Dyslipidemia
- Insulin resistance, asymptomatic hyperglycemia
- Rapidly progressive ascending neuromuscular weakness (rare)

Special Instructions

- Stavudine can be given without regard to food.
- Shake stavudine oral solution well before use. Keep refrigerated; the solution is stable for 30 days.

Metabolism/Elimination

- Renal excretion 50%. Decrease dose in renal dysfunction.
- Stavudine is phosphorylated intracellularly to the active metabolite stavudine triphosphate.

Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- *Renal elimination:* Drugs that decrease renal function could decrease stavudine clearance.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Stavudine **should not be administered** in combination with zidovudine because of virologic antagonism.
- *Overlapping toxicities:* The combination of stavudine and didanosine **is not recommended** because of overlapping toxicities. Reported toxicities occur more frequently in adults and include serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women.
- *Ribavirin and interferon:* Hepatic decompensation (sometimes fatal) has occurred in patients with HIV/hepatitis C virus co-infection who are receiving antiretroviral therapy (ART), interferon, and ribavirin.
- *Doxorubicin:* Simultaneous use of doxorubicin and stavudine should be avoided. Doxorubicin may inhibit the phosphorylation of stavudine to its active form.

Major Toxicities

- *More common:* Headache, gastrointestinal disturbances, skin rashes, hyperlipidemia, and fat maldistribution.
- *Less common (more severe):* Peripheral sensory neuropathy is dose-related. It occurs more frequently in patients with advanced HIV disease, a prior history of peripheral neuropathy, and in patients receiving other drugs associated with neuropathy. Pancreatitis. Lactic acidosis and severe hepatomegaly with hepatic steatosis, including fatal cases, have been reported.[1-3] The combination of stavudine and didanosine may result in enhanced toxicity (increased risk of fatal and nonfatal cases of lactic acidosis, pancreatitis, peripheral neuropathy, and hepatotoxicity), particularly in adults, including pregnant women—**this combination should not be used**. Risk factors found to be associated with lactic acidosis in adults include female sex, obesity, and prolonged nucleoside exposure.[4]
- *Rare:* Increased liver enzymes and hepatic toxicity, which may be severe or fatal. Neurologic symptoms, including rapidly progressive ascending neuromuscular weakness, are most often seen in the setting of lactic acidosis. Noncirrhotic portal hypertension with prolonged exposure.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

Although stavudine is Food and Drug Administration (FDA)-approved for use in infants aged ≥14 days and children, it **is no longer recommended** for use by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV because it carries a higher risk of adverse effects associated with mitochondrial toxicity and a higher incidence of lipoatrophy than other NRTIs.

Efficacy

Data from multiple pediatric studies of stavudine administered alone or in combination with other antiretroviral (ARV) agents demonstrate that stavudine is associated with clinical and virologic response.[5-11] In resource-limited countries, stavudine is frequently a component of initial ART in children, given with lamivudine and nevirapine. Stavudine is often a component of fixed-dose combinations that are not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 T lymphocyte (CD4) cell count and complete viral suppression in 50% to 80% of treatment-naive children.[12-15] In such a setting, where pediatric patients are already predisposed to anemia because of malnutrition, parasitic infestations, or sickle cell anemia, stavudine carries a lower risk of hematologic toxicity than zidovudine, especially in patients receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis.[16] Short-term use of stavudine in certain settings where access to other ARVs may be limited remains an important strategy for treating HIV in children.[17,18]

Toxicity

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.[19,20] In a large pediatric natural history study (PACTG 219C), stavudine-containing regimens had a modest—but significantly higher—rate of clinical and laboratory toxicities than regimens containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use.[20]

Lipodystrophy and Metabolic Abnormalities

Lipodystrophy syndrome (LS), and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with NRTIs, particularly stavudine, in adults and children.[21-24] Stavudine use has consistently been associated with a higher risk of lipodystrophy and other metabolic abnormalities (e.g., insulin resistance) in multiple pediatric studies involving children.[25-33] Improvements in (or resolution of) lipodystrophy were reported in 22.9% to 73% of cases after discontinuation of stavudine in two separate studies.[30,34]

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine.[1-3]

Mechanism

Many of the stavudine-related adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA in fat, muscle, peripheral blood mononuclear cells, and other tissues.[1,35-37] In a recent analysis involving a large cohort of pediatric patients (PACTG protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.[38]

World Health Organization Recommendations

The World Health Organization (WHO) cautions against using doses of stavudine that exceed 30 mg twice daily. This is in contrast to the FDA-recommended dose of 40 mg twice daily in patients weighing 60 kg or more.[39,40] Studies comparing the efficacy and toxicity of the two doses have consistently shown that both doses have similar efficacy. However, while the 30-mg dose shows lower toxicity than the 40-mg dose, the overall incidence of toxicity with the 30-mg dose is considered to be unacceptably high.[41-45] WHO recommends that stavudine be phased out of use in all patients because of concerns about unacceptable toxicity, even at the lower dose. Safer alternative agents can be prescribed.

Pharmacokinetics

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.[46] Although WHO has recommended using a reduced dose in adults, a similar dose reduction has not been suggested in children. A reduced pediatric dose has been proposed based on PK modeling, but clinical data on intracellular concentrations of the active stavudine triphosphate are lacking.[47,48] Intracellular stavudine triphosphate concentrations have not been measured in neonates.

Formulations

The pediatric formulation for stavudine oral solution requires refrigeration and has limited stability once reconstituted. As an alternative dosing method for children, capsules can be opened and dispersed in a small amount of water, with the appropriate dose drawn up into an oral syringe and administered immediately. Because plasma exposure of stavudine is equivalent whether the drug is administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.[49]

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Tipranavir (TPV, Aptivus) (Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Oral Solution: 100 mg tipranavir/mL, with 116 International Units (IU) vitamin E/mL

Capsules: 250 mg

Dosing Recommendations

Note: Tipranavir must be boosted with ritonavir. The ritonavir boosting dose used for tipranavir is higher than the doses used for other protease inhibitors.

Pediatric (Aged <2 Years) Dose:

- Not approved for use in children aged <2 years

Pediatric (Aged 2–18 Years) Dose:

Note: Not recommended for treatment-naive patients

Body Surface Area Dosing:

- Tipranavir/ritonavir (TPV/r) 375 mg/m^2/150 mg/m^2, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)

Weight-Based Dosing:

- TPV/r 14 mg/kg/6 mg/kg, both twice daily (maximum dose is TPV/r 500 mg/200 mg, both twice daily)

Adult Dose:

- TPV/r 500 mg (as two 250-mg capsules)/200 mg, both twice daily
- **Note:** Not recommended for treatment-naive patients

Selected Adverse Events

- Rare cases of fatal and non-fatal intracranial hemorrhage
- Skin rash (more common in children than adults)
- Nausea, vomiting, diarrhea
- Hepatotoxicity: elevated transaminases; clinical hepatitis
- Hyperlipidemia
- Hyperglycemia
- Elevated creatine phosphokinase

Special Instructions

- Administer tipranavir and ritonavir together and with food.
- Tipranavir oral solution contains 116 IU vitamin E per mL, which is significantly higher than the reference daily intake for vitamin E. Patients taking the oral solution should avoid taking any form of supplemental vitamin E that contains more vitamin E than found in a standard multivitamin.
- Tipranavir contains a sulfonamide moiety and should be used with caution in patients with sulfonamide allergy.
- Store tipranavir oral solution at room temperature, 25°C (77°F); do not refrigerate or freeze. Oral solution must be used within 60 days after the bottle is first opened.
- Store unopened bottles of oral tipranavir capsules in a refrigerator at 2°C to 8°C (36°F to 46°F). Once the bottle has been opened, capsules can be kept at room temperature (maximum of 77°F or 25°C) if used within 60 days.
- Use tipranavir with caution in patients who may be at increased risk of intracranial hemorrhage, including individuals with brain

lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcoholism, or who use anticoagulant or antiplatelet agents (including vitamin E).

- Use of tipranavir is contraindicated in patients with moderate or severe hepatic impairment.

Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inducer and substrate
- P-glycoprotein substrate

Tipranavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required.

Tipranavir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is required for mild hepatic impairment.
- Use of tipranavir is **contraindicated** in patients with moderate-to-severe hepatic impairment.

Drug Interactions (see also the Adult and Adolescent Guidelines and HIV Drug Interaction Checker)

- Tipranavir has the potential for multiple drug interactions. Co-administration of tipranavir/ritonavir (TPV/r) with drugs that are highly dependent on cytochrome P (CYP) 3A for clearance or are potent CYP3A inducers is contraindicated.
- Before tipranavir is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.
- TPV/r is a potent enzyme inducer and has the potential to decrease plasma concentrations of other antiretroviral drugs. TPV/r significantly decreases plasma concentrations of etravirine. Etravirine and TPV/r **should not be co-administered**.
- TPV/r has been shown to decrease raltegravir concentrations. TPV/r dose adjustment is not currently recommended when raltegravir is administered twice daily. However, TPV/r **should not be co-administered** with raltegravir HD once daily because significantly lower raltegravir concentrations are likely to occur.
- Tipranavir should be used with caution in patients who are receiving medications known to increase the risk of bleeding, such as antiplatelet agents, anticoagulants, or high doses of supplemental vitamin E.

Major Toxicities

- *More common:* Diarrhea, nausea, fatigue, headache, rash (which is more frequent in children than in adults), and vomiting. Elevated transaminases, cholesterol, and triglycerides. Elevated creatine phosphokinase.
- *Less common (more severe):* Lipodystrophy. Hepatotoxicity: clinical hepatitis and hepatic decompensation, including some fatalities. Patients with chronic hepatitis B or hepatitis C coinfection or elevations in transaminases are at increased risk of developing further transaminase elevations or hepatic

decompensation (approximately 2.5-fold risk). Epistaxis, which is more common with oral solution than capsule formulation.

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs. Increased risk of intracranial hemorrhage. Tipranavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other medical conditions.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval and General Considerations

Tipranavir is approved for use in children aged as young as 2 years and is available in a liquid formulation. Its indication is limited to those patients who are treatment-experienced and who have HIV strains that are resistant to more than one protease inhibitor (PI).[1] Tipranavir imposes a high pill burden on patients taking tipranavir capsules and requires a higher dose of boosting ritonavir than the doses used with other PIs. This increased dose of ritonavir is associated with a greater potential for drug interactions and increased toxicity. In addition, tipranavir is associated with serious adverse events (AEs) that limit its use to patients with few treatment options.

Efficacy

The Food and Drug Administration's approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of TPV/r in children with HIV (PACTG 1051/BI-1182.14).[2] This study enrolled 110 treatment-experienced children (with the exception of three treatment-naive patients) aged 2 years to 18 years (with a median age of 11.7 years). Patients were randomized to receive two different dosing regimens. The higher dose of TPV/r (375 mg/150 mg/m^2 body surface area [BSA] twice daily) plus optimized background therapy was associated with better virologic responses at 48 weeks, particularly in the older, more heavily pretreated patients, when compared to the lower dose that was studied. A follow-up study of PACTG 1051 participants evaluated the long-term safety, efficacy, and tolerability of TPV/r in pediatric patients.[3] At Week 288, most children were no longer receiving TPV/r. Reasons for discontinuation included AEs, virologic failure, and nonadherence. The youngest patients who were stable at Week 48 were more likely to still be on treatment after 5 years with continued efficacy.[3]

Pharmacokinetics

PK evaluation of the liquid formulation at steady state in children was assessed.[4] In children aged 2 to <12 years, a dose of TPV/r 290 mg/115 mg/m^2 BSA achieved tipranavir trough concentrations that were consistent with those achieved in adults receiving standard TPV/r 500 mg/200 mg dosing. However, children aged 12 to 18 years required a higher dose (375 mg/150 mg/m^2 BSA, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that seen in adults receiving the standard TPV/r dose. Based on available data, a dose of TPV/r 375 mg/150 mg/m^2 BSA twice daily is recommended.

Toxicity

AEs were similar between treatment groups in the multicenter, pediatric study.[2] Twenty-five percent of children experienced a drug-related serious AE, and 9% of patients discontinued study drugs because of AEs. The most common AEs were gastrointestinal disturbances: 37% of participants had vomiting and 24% had diarrhea. The most common Grade 3 through 4 laboratory abnormalities were increases in the levels of creatine phosphokinase (11% of participants), alanine aminotransferase (6.5% of participants), and amylase (7.5% of participants). In the long-term follow-up report for PACTG 1051, incidence of AEs defined as drug-related was 55% to 65% regardless of age at entry, with higher discontinuation rates due to AEs in the older age groups.[3]

Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 international units (IU) of vitamin E and 100 mg tipranavir per mL of solution. The recommended dose of tipranavir (14 mg/kg body weight) results in a vitamin E dose of 16 IU/kg body weight per day, significantly higher than the reference daily intake for vitamin E (which is 30 IU for adults and approximately 6–22 IU for children and adolescents, depending on age of the child or adolescent) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%).[2] Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.[5]

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Appendix B: Acronyms

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
BIC	bictegravir
CAB	cabotegravir
COBI or /c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DMPA	depot medroxyprogesterone acetate
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IBA	ibalizumab
IDV	indinavir
INH	isoniazid
LPV	lopinavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RBV	ribavirin
RPV	rilpivirine
RTV or /r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
THAM	tris (hydroxymethyl) aminomethane

Abbreviation	Full Name
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TMP-SMX	trimethoprim sulfamethoxazole
TPV	tipranavir
ZDV	zidovudine

General Terms

Acronym	Term
° C	degrees Celsius
° F	degrees Fahrenheit
25-OH-vitamin D	25-hydroxy vitamin D
AE	adverse effect or adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ART	antiretroviral therapy
ARV	antiretroviral
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{12h}	12-hour area under the curve
AUC_{24h}	24-hour area under the curve
AUC_{tau}	area under the concentration time curve over the dosing interval
AV	atrioventricular
BCRP	breast cancer resistance protein
BMD	bone mineral density
BMI	body mass index
BSA	body surface area
C_{0h}	pre-dose concentration
C_{12h}	concentration at 12 hours
C_{24h}	concentration at 24 hours
CBC	complete blood count
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CK	creatine kinase
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CT	continuous therapy or continuous treatment
C_{tau}	concentration at the end of a dosing interval
C_{trough}	trough concentration
CT_x	C-telopeptide of type 1 collagen
CV	coefficient of variation
CVD	cardiovascular disease

Acronym	Term
CYP	cytochrome P450
dL	deciliter
DAIDS	Division of AIDS (NIAID)
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DOT	directly observed therapy
DRESS	drug reaction (or rash) with eosinophilia and systemic symptoms
DSG	delayed switch group
DSMB	Data Safety Monitoring Board
DXA	dual energy X-ray absorptiometry
EBV	Epstein-Barr virus
EC	enteric-coated
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EM	erythema multiforme or extensive metabolizers
FDA	U.S. Food and Drug Administration
FDC	fixed-dose combination
fL	femtoliter
FLP	fasting lipid profile
fmol	femtomole
FPG	fasting plasma glucose
g	gram
G6PD	glucose-6-phosphate dehydrogenase
GA	gestational age
GFR	glomerular filtration rate
GI	gastrointestinal
GLSM	geometric least squares mean
GM	geometric mean
GMR	geometric mean ratio
gp120	Glycoprotein 120
h	hour
HA	height age
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
HgbA1c	glycosylated hemoglobin

Acronym	Term
HHS	Department of Health and Human Services
HIV RNA or HIV-1 RNA	viral load
HLA	human leukocyte antigen
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
HSV	herpes simplex virus
IAS–USA	International Antiviral Society–USA
IFPG	impaired fasting plasma glucose
IGT	impaired glucose tolerance
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IQR	interquartile range
IR	insulin resistance
IRIS	immune reconstitution inflammatory syndrome
ISG	immediate switch group
IU	international units
IV	intravenous
IVIG	intravenous immune globulin
kg	kilogram
L	liter
LAI	long-acting injectable
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
$\log_{10}$	the logarithm to the base 10
LS	lipodystrophy syndrome
LVH	left ventricular hypertrophy
m^2	square meter
mcg	microgram
MCV	mean cell volume
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm^3	cubic millimeter
mmol	millimole
N/A	not available or not applicable
NASBA	nucleic acid sequence-based amplification
NAT	nucleic acid test
ng	nanogram
nM	nanometer

Acronym	Term
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTD	neural tube defect
OARAC	Office of AIDS Research Advisory Council
OATP	organic anion transporter polypeptide
OBT	optimized background therapy
OGTT	oral glucose tolerance test
OI	opportunistic infection
oz	ounce
PA-IC_{95}	protein-adjusted IC_{95}
PBMC	peripheral blood mononuclear cell
PCP	*Pneumocystis jirovecii* pneumonia
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PG	plasma glucose
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PPI	proton pump inhibitor
PUFA	polyunsaturated fatty acid
QTc	corrected QT
RNA	ribonucleic acid
RPG	random plasma glucose
RT-PCR	reverse transcription polymerase chain reaction
SAM	severe acute malnutrition
SCT	short-cycle therapy
SD	standard deviation
SJS	Stevens-Johnson syndrome
SM	slow metabolizers
SMR	sexual maturity rating
SQ	subcutaneous
STI	sexually transmitted infection
STR	single-tablet regimen
$T_{½}$	half-life
TB	tuberculosis
TBLH	total body less head
TC	total cholesterol
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrolysis

Acronym	Term
TG	triglyceride
T_{max}	time to reach maximum concentration
U = U	Undetectable = Untransmittable
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
v/v	volume per volume
v/w	volume per weight
WHO	World Health Organization
XR	extended release

Study and Trial Names

Acronym	Name
ACTG	AIDS Clinical Trials Group
ANRS	National Agency for AIDS Research (France)
ARROW	Anti-retroviral research for Watoto
ATHENA	AIDS Therapy Evaluation in the Netherlands
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
ATN	Adolescent Trials Network
CHAPAS	Children with HIV in Africa—Pharmacokinetics and Acceptability of Simple second-line antiretroviral regimens
CHER	Children with HIV Early Antiretroviral Therapy
DIONE	A Study to Evaluate Antiviral Activity of Darunavir + Ritonavir in HIV-1 Infected Adolescents
ENCORE	Evaluation of Novel Concepts in Optimization of antiRetroviral Efficacy
FLAIR	First Long-Acting Injectable Regimen
HPPM	HIV Paediatric Prognostic Markers
HPTN	HIV Prevention Trials Network
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials
MOCHA	More Options for Children and Adolescents
NEVEREST	Nevirapine Resistance Study
PACTG	Pediatric AIDS Clinical Trials Group
PENPACT	Trial run in collaboration between PENTA and PACTG/IMPAACT
PENTA	Paediatric European Network for Treatment of AIDS
PHACS	Pediatric HIV/AIDS Cohort Study
PREDICT	Early Versus Deferred Antiretroviral Therapy for Children Older Than 1 Year Infected with HIV
PROMOTE	PEPFAR PROMise Ongoing Treatment Evaluation
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SMILE	Strategy for Maintenance of HIV Suppression With Once Daily Integrate Inhibitor+Darunavir/Ritonavir in Children
START	Strategic Timing of AntiRetroviral Treatment

Appendix C: CDC Pediatric HIV CD4 Cell Count/Percentage and HIV-Related Diseases Categorization

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Table A. HIV Infection Stage Based on Age-Specific CD4 Count or Percentage

Stage[a]	Aged <1 Year		Aged 1 Year to <6 Years		Aged ≥6 Years	
	Cells/mm^3	%	Cells/mm^3	%	Cells/mm^3	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a] The stage is based primarily on the CD4 count; the CD4 count takes precedence over the CD4 percentage, and the percentage is considered only when the count is missing. If a Stage 3–defining condition has been diagnosed (see Table 6), then the stage is 3, regardless of CD4 test results.

Key: CD4 = CD4 T lymphocyte

Source: Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR* 2014;63(No. RR-3):1-10.

Table B. HIV-Related Symptoms and Conditions

Mildly Symptomatic
Children with two or more of the following conditions, but none of the conditions listed in the Moderately Symptomatic category, are considered mildly symptomatic: • Lymphadenopathy (lymph nodes are ≥0.5 cm at more than two sites and/or bilateral at one site) • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Moderately Symptomatic
• Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000 per µL [<1.0 × 10^9 per L]), and/or thrombocytopenia (platelet count <100 × 10^3 per µL [<100 × 10^9 per L]) persisting for ≥30 days • Bacterial meningitis, pneumonia, or sepsis (single episode)

- Candidiasis, oropharyngeal (thrush), persisting for >2 months in children aged >6 months
- Cardiomyopathy
- CMV infection, with onset before age 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- HSV stomatitis, recurrent (more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before age 1 month
- Varicella, disseminated (complicated chickenpox)

AIDS-Defining Conditions

- Bacterial infections, multiple or recurrent[a]
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1-month duration)
- CMV disease (other than liver, spleen, or lymph nodes), onset at age >1 month
- CMV retinitis (with loss of vision)
- Encephalopathy attributed to HIV[b]
- HSV: chronic ulcers (>1-month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary (of brain)
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary

- *Mycobacterium* tuberculosis of any site, pulmonary, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia
- Pneumonia, recurrent[c]
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV[b]

[a] Only among children aged <6 years.

[b] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(No. RR-12).

Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR.* 1992;41(No. RR-17).

[c] Only among adults, adolescents, and children aged ≥6 years.

Key: CMV = cytomegalovirus; HSV = herpes simplex virus

Modified from:

Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR.* 1994;43(No. RR-12).

Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

Appendix D: Supplemental Information

Updated: Apr.11, 2022
Reviewed: Apr.11, 2022

Table A. Likelihood of Developing AIDS or Death Within 12 Months, by Age and CD4 T-Cell Percentage or Log_{10} HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

	CD4 Percentage				Log_{10} HIV RNA Copy Number		
Age	**10%**	**20%**	**25%**	**30%**	**6.0**	**5.0**	**4.0**
Percent Mortality (95% Confidence Interval)							
6 Months	28.7	12.4	8.5	6.4	9.7	4.1	2.7
1 Year	19.5	6.8	4.5	3.3	8.8	3.1	1.7
2 Years	11.7	3.1	2.0	1.5	8.2	2.5	1.1
5 Years	4.9	0.9	0.6	0.5	7.8	2.1	0.7
10 Years	2.1	0.3	0.2	0.2	7.7	2.0	0.6
Percent Developing AIDS (95% Confidence Interval)							
6 Months	51.4	31.2	24.9	20.5	23.7	13.6	10.9
1 Year	40.5	20.9	15.9	12.8	20.9	10.5	7.8
2 Years	28.6	12.0	8.8	7.2	18.8	8.1	5.3
5 Years	14.7	4.7	3.7	3.1	17.0	6.0	3.2
10 Years	7.4	2.2	1.9	1.8	16.2	5.1	2.2

Note: Table modified from: HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet*. 2003;362:1605-1611.

Table B. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Cell Count andAge in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)

Age (Years)	Absolute CD4 Cell Count (cells/mm^3)					
	<50	**50–99**	**100–199**	**200–349**	**350–499**	**500+**
Rate of Death Per 100 Patient-Years						
0–4	59.3	39.6	25.4	11.1	10.0	3.5
5–14	28.9	11.8	4.3	0.89	0.00	0.00
15–24	34.7	6.1	1.1	0.71	0.58	0.65
25–34	47.7	10.8	3.7	1.1	0.38	0.22
35–44	58.8	15.6	4.5	0.92	0.74	0.85
45–54	66.0	18.8	7.7	1.8	1.3	0.86
55+	91.3	21.4	17.6	3.8	2.5	0.91

Rate of AIDS or Death per 100 Patient-Years						
0–4	82.4	83.2	57.3	21.4	20.7	14.5
5–14	64.3	19.6	16.0	6.1	4.4	3.5
15–24	61.7	30.2	5.9	2.6	1.8	1.2
25–34	93.2	57.6	19.3	6.1	2.3	1.1
35–44	88.1	58.7	25.5	6.6	4.0	1.9
45–54	129.1	56.2	24.7	7.7	3.1	2.7
55+	157.9	42.5	30.0	10.0	5.1	1.8

Note: Table modified from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis.* 2008;197:398-404.

Table C. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children[a]

Baseline HIV RNA[c] (Copies/mL) Baseline CD4 Percentage	No. Patients[d]	Deaths[b]	
		Number	Percentage
≤100,000			
≥15%	103	15	(15%)
<15%	24	15	(63%)
>100,000			
≥15%	89	32	(36%)
<15%	36	29	(81%)

[a] Data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

[b] Mean follow-up: 5.1 years.

[c] Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

[d] Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. J Infect Dis. 1997;175(5):1029–1038.

Figure A. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

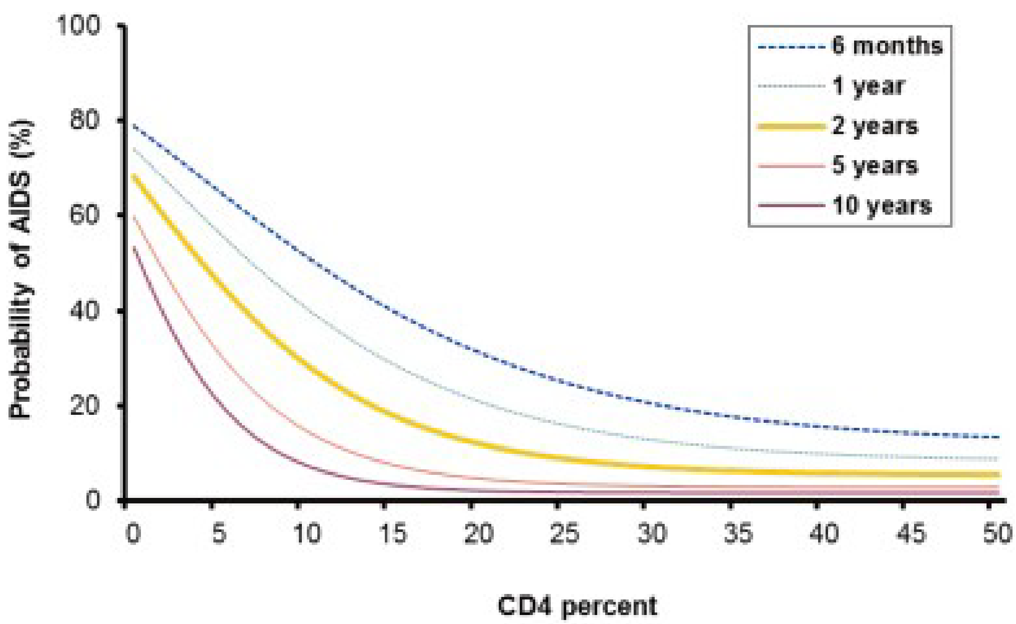

Figure modified from *Lancet* 2003;362:1605-1611

Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

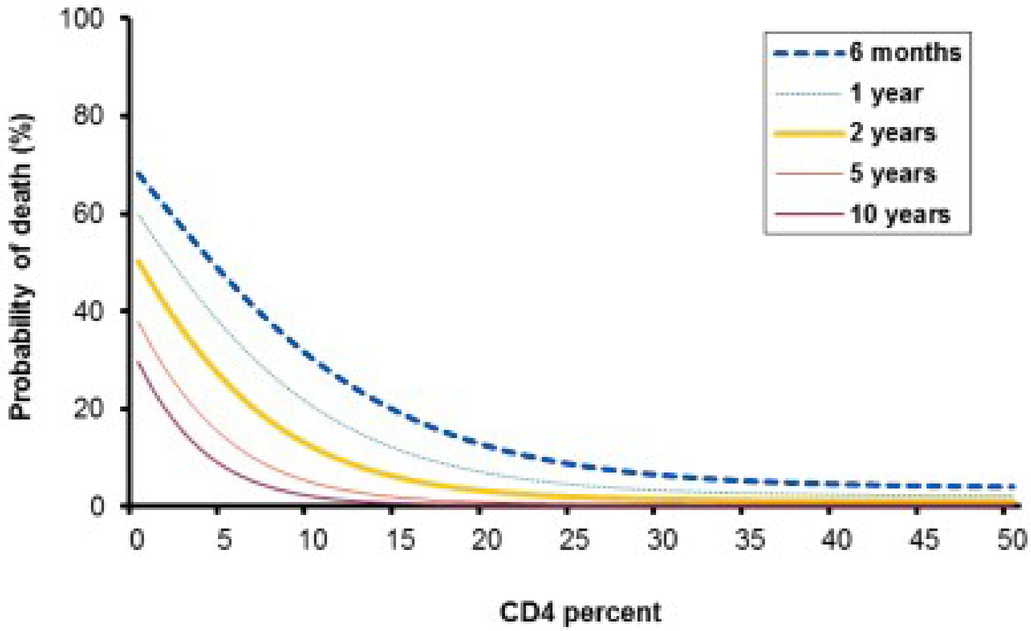

Figure modified from *Lancet* 2003;362:1605-1611

Figure C. Death Rate per 100 Person-Years in HIV-Infected Children Aged 5 Years or Older in the HIV Paediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study*

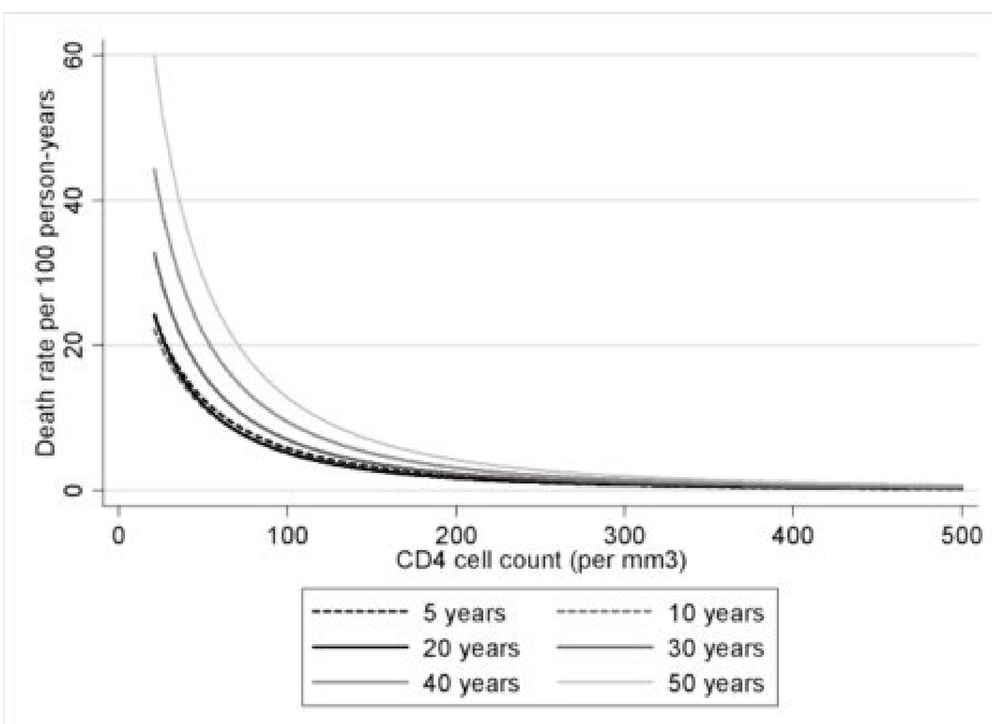

Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis.* 2008;197:398-404.

Figure D. Estimated Probability of AIDS Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

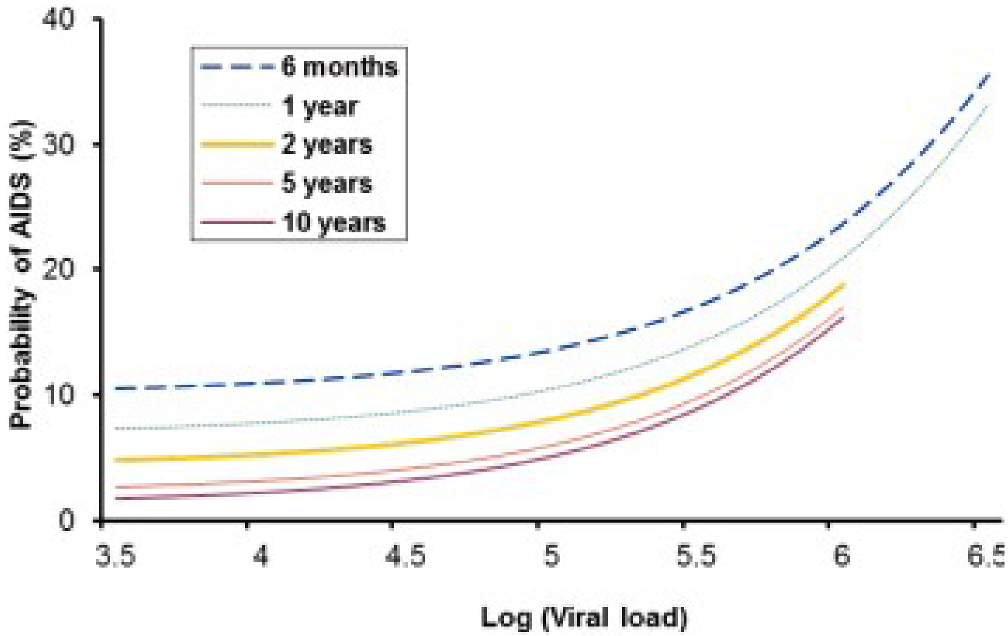

Figure modified from *Lancet* 2003;362:1605-1611

Figure E. Estimated Probability of Death Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy

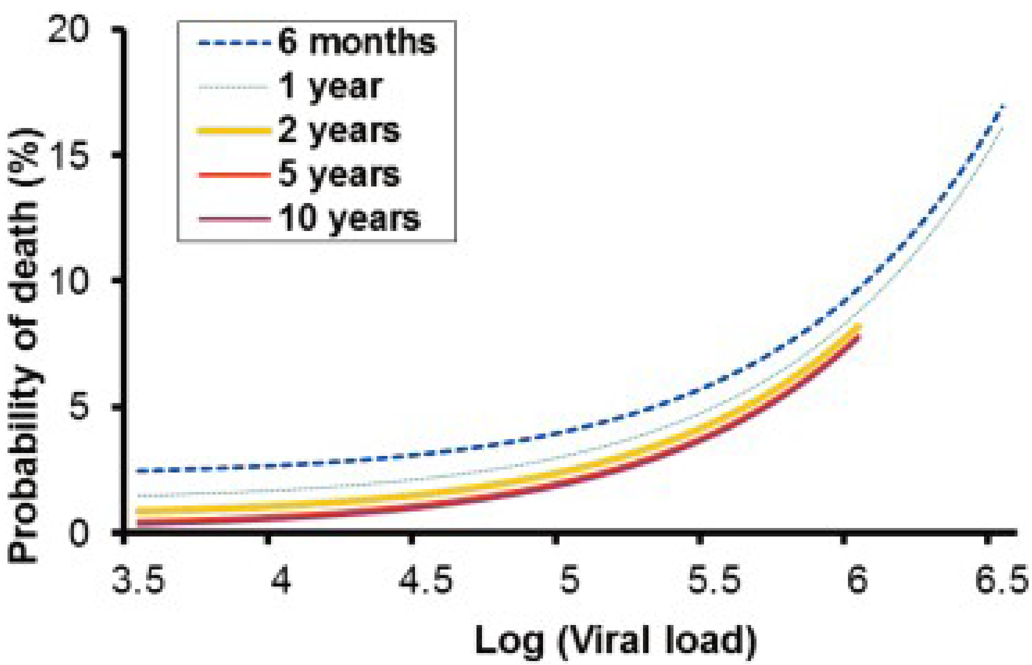

Figure modified from *Lancet* 2003;362:1605-1611