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. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed (insert date) [include page numbers, table number, etc. if applicable]

Use of antiretrovirals in pediatric patients is evolving rapidly. These guidelines are updated regularly to provide current information.The most recent information is available at http://aidsinfo.nih.gov.

What's New in the Pediatric Guidelines <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

The Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (Pediatric Guidelines) are published in an electronic format that can be updated as relevant changes in prevention and treatment recommendations occur. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) is committed to making timely changes to this document because so many health care providers, patients, and policy experts rely on it for vital clinical information.

Major revisions made to the Pediatric Guidelines within the last 12 months are as follows:

April 16, 2019

The Panel updated the text and references of the May 22, 2018 Pediatric Guidelines to include relevant new data and publications. Key updates are summarized below.

Safety Concerns About the Use of Dolutegravir at the Time of Conception and During Pregnancy

Data from a National Institutes of Health-funded, observational surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana suggest that there is a possible increased risk of neural tube defects in infants born to women who were receiving dolutegravir at the time of conception. Further data collection is ongoing, and additional analyses will be required to confirm this potential safety signal. Before patients become sexually active, pediatric and adolescent providers should discuss the potential risk of neural tube defects with patients who are receiving or initiating dolutegravir and their caregivers. The sections listed below provide links to additional information and specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

- What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children
- Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV
- Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy
- Recognizing and Managing Antiretroviral Treatment Failure
- Dolutegravir
- Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents

Introduction

- The Panel notes that children living with HIV in the United States are increasingly foreign-born; 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 to their countries of origin, and legal and psychosocial needs related to immigration.

Maternal HIV Testing and Identification of Perinatal HIV Exposure

- The Panel has made minor edits and corrections to the version of this section that was published on December 14, 2018.

When to Initiate Therapy in Antiretroviral-Naive Children

- Boxed recommendations have been added to When to Initiate Therapy in Antiretroviral-Naive Children.
- The Panel recommends initiating ART in all treatment-naive infants and children with HIV infection and has updated wording to recommend rapid initiation of treatment (within 1-2 weeks) with an expedited discussion of adherence for children aged ≥6 weeks to <12 weeks and for children of any age with immunodeficiency or opportunistic illnesses that indicate Stage 3 HIV infection according to the Centers for Disease Control and Prevention. In other situations, sufficient time to fully assess and address issues associated with adherence should be allowed prior to ART initiation.
- Every 3 to 4 months, health care providers should monitor the virologic, immunologic, and clinical status of any child with HIV infection who does not initiate ART **(AIII)**.

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

- Table 7. Antiretroviral Regimens Recommended for <u>Initial</u> Therapy for HIV Infection in Children and the associated text now include updated Panel recommendations that reflect new weight parameters for use of some drugs in children. The revised recommendations are summarized below.
  - The fixed dose combination (FDC) tablet elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) or dolutegravir plus two nucleoside reverse transcriptase inhibitors (NRTIs) are now *Preferred* integrase strand transfer inhibitor (INSTI)-based regimens for children weighing ≥25 kg **(AI)**.
  - Raltegravir plus two NRTIs is now classified as a *Preferred* INSTI-based regimen for children weighing <25 kg and as an *Alternative* INSTI-based regimen for children and adolescents weighing ≥25 kg.
  - Atazanavir/ritonavir plus two NRTIs is now classified as an *Alternative* protease inhibitor (PI)-based regimen for children aged ≥3 years and weighing ≥25 kg (AI).
  - Darunavir/ritonavir plus two NRTIs is now recommended as a *Preferred* PI-based regimen for children aged ≥3 years and weighing ≥10 kg but <25 kg, and as an *Alternative* PI-based regimen in children aged ≥3 years and weighing ≥25 kg **(AI*)**.
  - The FDC tablet emtricitabine/tenofovir alafenamide (Descovy) is now a *Preferred* dual-NRTI combination for children weighing ≥25 kg.

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

- Bictegravir and doravirine were added to this section because they are not yet approved by the Food and Drug Administration (FDA) for use in children.
- Older ARV drugs that the Panel **does not recommend** for use in children because of unacceptable toxicities, inferior virologic efficacy, pill burden, pharmacologic concerns, and/or limited pediatric data include didanosine, enfuvirtide, fosamprenavir, indinavir, nelfinavir, stavudine, saquinavir, and tipranavir. These drugs have been removed from this section. See the <u>Archived Drugs</u> section in the Pediatric Drug Information Appendix for additional information.

Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV

- The Panel recommends that all adolescents who are living with HIV should be screened for mental health disorders and substance use disorders **(AII)**.
- A new subsection was added about the mental health concerns of adolescents with perinatally acquired HIV.

Management of Medication Toxicity or Intolerance

- As more new ARV drugs are approved for use in children, many of the older ARV drugs are no longer recommended because of the toxicities associated with those agents. Several older ARV drugs—didanosine, enfuvirtide, fosamprenavir, indinavir, saquinavir, stavudine, and tipranavir—have been removed from the Management of Medication Toxicity or Intolerance tables, and the Peripheral Nervous System Toxicity Table has been deleted since it only contained information about some of these older drugs (didanosine, indinavir, and stavudine).
- Information on the toxicities that are associated with these older agents can be found in archived versions of the toxicity tables and the Archived Drugs section.
- The management section of the Dyslipidemia Toxicity Table has been revised.

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

- The section has been revised to add a new subsection on Treatment Simplification, and subheadings have been added for content about Treatment Optimization, Toxicity Management, and Regimens That Are Not Recommended for Use in Children.
- Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression has been updated.

Recognizing and Managing Antiretroviral Treatment Failure

- 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 has been updated.

Appendix A: Pediatric Antiretroviral Drug Information

Drug sections and Fixed-Dose Combination Tables 1 and 2 in this appendix were reviewed and updated to include new pediatric data and dosing and safety information, plus new formulations and FDCs. Significant changes are summarized below.

- For children who are receiving twice-daily liquid formulations of abacavir, the Panel no longer recommends a specific time frame for when clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts should switch from twice-daily to once-daily dosing. Previously, the Panel recommended making this switch at 6 months or 24 weeks.
- Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (Symfi) is now available, and this FDC tablet is approved by the FDA for use in children and adolescents weighing ≥40 kg.
- The Panel has added guidance about the use of efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (Symfi Lo) in children and adolescents weighing ≥40 kg with sexual maturity ratings of 1 to 3. Therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients weighing ≥40 kg.
- Etravirine is now approved by the FDA for use in ARV-experienced children aged ≥2 years and weighing ≥10 kg.
- The Panel recommends using an investigational dose of dolutegravir (50 mg) for children and adolescents weighing ≥25 kg who are ARV-naive or ARV-experienced but INSTI-naive and who are not being treated with uridine diphosphate glucuronyl transferase 1A1 or cytochrome P450 3A inducers. This recommended dose is based on interim data from ongoing trials that indicate that using the FDA-approved dose of dolutegravir 35 mg in patients weighing ≥30 kg to 40 kg may result in suboptimal trough concentrations. Dolutegravir is not approved by the FDA for use in children weighing <30 kg.
- Lopinavir/ritonavir (Kaletra) is approved by the FDA for use in neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, if no alternatives are

available for infants who have not met these age thresholds, some members of the Panel recommend using lopinavir/ritonavir oral solution immediately after birth in combination with careful monitoring; see the lopinavir/ritonavir section for additional information.

- The Panel has provided updated information about the investigational dosing of bictegravir/emtricitabine/ tenofovir alafenamide (Biktarvy) that is currently being studied in children aged 6 years to <12 years and weighing ≥25 kg, and children and adolescents aged 12 years to <18 years and weighing ≥35 kg; however, Biktarvy is not approved by the FDA for pediatric use.

- New sections were added for doravirine and ibalizumab; however, these drugs are not yet approved for use in children or adolescents aged <18 years.

- Older ARV drugs that the Panel **does not recommend** for use in children because of unacceptable toxicities, inferior virologic efficacy, pill burden, pharmacologic concerns, and/or limited pediatric data have been moved into an Appendix section titled Archived Drugs; data on these drugs will no longer be reviewed by the Panel. The drugs moved into this section include didanosine, enfuvirtide, fosamprenavir, indinavir, nelfinavir, saquinavir, stavudine, and tipranavir.

December 14, 2018

Updates to the guidelines include the addition of two new tables about fixed-dose combinations (FDCs) of antiretroviral (ARV) drugs in Appendix A: Pediatric Antiretroviral Drug Information and revisions to the three sections that are shared with *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission*.

Maternal HIV Testing and Identification of Perinatal HIV Exposure

- A new bulleted recommendation was added to emphasize that partners of pregnant women should be encouraged to undergo HIV testing if their HIV status is unknown.

- Risk of HIV exposure should be assessed in all women who are considering becoming pregnant, as well as in all pregnant women who previously tested HIV negative. Women with risk factors for HIV acquisition should receive prevention counseling and appropriate interventions, including pre-exposure prophylaxis, if indicated.

- The indications for third-trimester HIV retesting have been updated to include women who are incarcerated or who reside in states that require third-trimester testing. Data about gaps in perinatal HIV testing suggest that providers should be proactive in assessing a woman's HIV acquisition risk and implementing third-trimester HIV retesting in areas where it is not routine, when indicated.

Diagnosis of HIV Infection in Infants and Children

- The use of an assay that detects HIV non-B subtype viruses or Group O is now recommended for known or suspected maternal non-B subtype virus or Group O infections (RNA nucleic acid tests (NATs) and dual-target total DNA/RNA tests).

- The case definition for indeterminate HIV infection in children aged <18 months has been added.

Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV

- Zidovudine plus lamivudine plus raltegravir is now a recommended empiric HIV therapy option for neonates who are at a higher risk of perinatal HIV transmission. Information has been added to this section about the use and safety of raltegravir in infants.

- Some Panel members opt to discontinue nevirapine, raltegravir, and/or lamivudine when the birth HIV NAT returns negative, while others choose to continue empiric HIV therapy for 6 weeks. In all cases

where the newborn is at a higher risk of HIV acquisition, zidovudine should be continued for 6 weeks. The Panel recommends consulting with an expert in pediatric HIV when making a decision about the duration of empiric HIV therapy.

- Table 11. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 12. Newborn Antiretroviral Dosing Recommendations have been revised according to updated recommendations for the treatment of newborns with HIV infection and newborns who are at low risk or high risk of perinatal HIV transmission.

Appendix A: Pediatric Antiretroviral Drug Information

- Two new tables in Appendix A provide information about FDC formulations of ARV drugs and their use in children.

- Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets organizes information as grid, with ARV drugs listed alphabetically by class across the top and available FDCs listed on the left.

- Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents columns include dosages of FDC component drugs, the minimum body weight requirements for these drugs, pill size (when available), and food requirements.

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Members of Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

These updated *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* were developed by the Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) convened by the Office of AIDS Research Advisory Committee (OARAC) and supported by the Health Resources and Services Administration (HRSA); and the National Institutes of Health (NIH).

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Key to Abbreviations: C = Chair; DSMB = Data Safety Monitoring Board; ES = Executive Secretary; HHS = Member from Health and Human Services; M = Member; N/A = Not Applicable; NVO = Non-Voting Observer; VC = Vice Chair

Introduction

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 living with HIV, including adolescents with sexual maturity ratings (SMRs, formerly Tanner staging) 1 to 3 (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 [SMR 4–5]). These 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 provides regular updates to the guidelines. The guidelines are available on the AIDS*info* website.

The AIDS*info* website also provides separate guidelines for:

- The prevention and treatment of opportunistic infections (OIs) in children exposed to HIV and children with HIV infection;[1]
- The use of ARV drugs in adolescents and adults with HIV;[2]
- The use of ARV drugs in pregnant women with HIV;[3] *and*
- The prevention and treatment of OIs in adolescents and adults with HIV.[4]

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 content that is closely related and that sometimes overlaps. To ensure that information is consistent across the guidelines and that users can easily find the information they need, the Panels of these two 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 authors 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 Perinatal HIV

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 living with HIV in the United States. The widespread use of ARV drugs in pregnant women living with HIV and the use of ARV prophylaxis in infants who have been exposed to HIV have together reduced vertical transmission rates to less than 2%, with fewer than 50 new infant infections estimated for the United States in 2014.[5] Since the introduction of combination ART, mortality in children with perinatal HIV infection has decreased by more than 80% to 90%, and opportunistic and other related infections in children have significantly declined.[6,7] Children living with HIV are less likely to develop AIDS because of routine and early initiation of effective ART.[8,9] ARV drug-resistance testing has made it easier for clinicians to choose effective initial and subsequent regimens. Treatment strategies continue to focus on timely initiation of ART regimens that are capable of maximally suppressing viral replication to 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 ART regimens for children, especially infants.[10] Children living with HIV in the United States are increasingly

foreign-born; 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 living with HIV grow older, there are new challenges 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]

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

- Acquisition of infection through perinatal exposure for most children living with HIV;
- *In utero* and neonatal exposure to ARV drugs in most children with perinatal HIV infection;[15]
- The need to use HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months old;
- Age-specific interpretation 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;
- Changes in PK parameters with age, caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance;[16]
- 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 living 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, clinical trials are critically needed to 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 infection. Because of the complexity of caring for children with HIV, and the decreasing number of children with perinatally acquired HIV in the United States, 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 phone consultation. The Center can be contacted at (800) 933-3413, 9 am to 8 pm EST, Monday through Friday.[17]

Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the Guidelines	The guidelines provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in infants, children, and adolescents in early to mid-puberty (sexual maturity rating [SMR] 1-3) who are living with HIV in the United States.

Table 1. Outline of the Guidelines Development Process, continued

Topic	Comment
Panel Members	The Panel is composed of approximately 35 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 living 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 (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, *ex officio* member 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 AIDS*info* website.
Users of the Guidelines	Providers of care to infants, children, and adolescents living 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)
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 section working groups. The recommendations are generally 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) who are living 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 pregnant women with HIV infection (including maternal and infant interventions to prevent perinatal transmission), ART for nonpregnant adults and postpubertal adolescents with HIV infection, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*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 significant 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 AIDS*info* website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be 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 AIDS*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 contactus@aidsinfo.nih.gov.

Basis for Recommendations

Recommendations in these guidelines are based upon 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 ARV drugs to use in children often rely, in part, on data from clinical trials or studies in adults. Pediatric drug approval may be based on evidence from adequate and well-controlled investigations in adults if:

- The course of the disease and the effects of the drug in the pediatric and adult populations are expected to be similar enough to permit extrapolation of adult efficacy data to pediatric patients;

- 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 there is a concern 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, there is much more substantial and higher-quality evidence related to the use of ARV drugs from studies in adults (especially randomized clinical trials) than 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 long-term 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 that there is a clinical benefit to initiating treatment at a certain CD4 cell count and data from smaller observational studies in children indicate that 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 that is available to guide the management of HIV infection in children, clinicians are encouraged to discuss available trials with children and their caregivers. Information about clinical trials for adults and children with HIV can be obtained from the AIDS*info* website or by telephone at (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 long-term clinical outcomes
	II: One or more well-designed, nonrandomized trials or observational cohort studies **in children**[a] with long-term clinical outcomes
	II*: One or more well-designed, nonrandomized trials or observational cohort studies **in adults** with long-term 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
(Last updated April 16, 2019; last reviewed April 16, 2019)

Panel's Recommendations
• HIV testing is recommended as standard of care for all sexually active women and should be a routine component of preconception care **(AII)**.
• All pregnant women 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) **(AII)**.
• Partners of pregnant women should be encouraged to undergo HIV testing when their status is unknown **(AIII)**.
• Repeat HIV testing in the third trimester is recommended for pregnant women with negative initial HIV antibody tests who are at increased risk of acquiring HIV, including those who are 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, or those who reside in states that require third-trimester testing (see Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings **(AII)**.
• Expedited HIV testing at the time of labor or delivery should be performed for any woman with undocumented HIV status; testing should be available 24 hours a day, and results should be available within 1 hour **(AII)**. If results are positive, intrapartum antiretroviral (ARV) prophylaxis should be initiated immediately **(AI)**, and infants should receive an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission as soon as possible, pending results of supplemental HIV testing **(AII)**. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for guidance.
• Women who have not been 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)**. If the results for the mother or infant are positive, an appropriate infant ARV drug regimen should be initiated immediately, and the mother should not breastfeed unless supplemental HIV testing is negative **(AII)**. Infants with initial positive HIV viral tests (RNA, DNA) should have their ARV regimen modified, if necessary, to a three-drug combination of ARV drugs at treatment doses (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV) **(AII)**.
• 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 to determine HIV status is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown **(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* |

HIV Testing in Pregnancy

HIV infection should be identified prior to pregnancy (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV) or as early in pregnancy as possible. This provides the best opportunity to improve maternal health and pregnancy outcomes, to prevent infant acquisition of HIV, and to identify HIV infection and 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 women in the United States by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV and the Panel on Treatment of Pregnant Women with HIV Infection 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.[1-5] All HIV testing should be performed in a manner that is consistent with state and local laws. The CDC recommends the "opt-out" approach, which involves notifying pregnant women that HIV testing will be performed as part of routine

care unless they choose not to be tested for HIV.[2] The "opt-out" approach during pregnancy is allowed in some jurisdictions.[6] The "opt-in" approach involves obtaining specific consent before testing, and this approach has been associated with lower testing rates.[7,8] The mandatory newborn HIV testing approach, adopted by several states, involves testing newborns for perinatal HIV exposure with or without maternal consent if the mother has declined prenatal or intrapartum testing.

Partners of pregnant women should also be encouraged to undergo 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 found to have HIV infection. Because women are more susceptible to HIV acquisition during pregnancy and the postpartum period,[9] clinicians can also initiate a discussion about preventative interventions, including pre-exposure prophylaxis, if the pregnant woman is uninfected. In addition, clinicians should assess the risk of acute HIV infection, particularly in late in pregnancy, because a pregnant woman may receive a negative result by expedited or rapid HIV testing when she is in the window period. However, during this period she would be viremic with high risk of perinatal transmission to her newborn. 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.[10-13] As discussed in the following sections, maternal HIV testing should be performed as early as possible during pregnancy, with repeat HIV testing in the third trimester for women who are at increased risk of acquiring HIV or who are living in areas of high HIV incidence. Women with unknown or undocumented HIV status should be tested during labor or after delivery.[10-13] Determining antenatal maternal HIV status enables:

- Women living with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections;

- Initiation of treatment in the identified women, which may also decrease the risk of transmission to their partners;[2,14,15]

- Referral of partners without HIV for preventative interventions;

- Provision of ART to the mother during pregnancy and labor, and provision of antiretroviral (ARV) drug prophylaxis to the newborn to reduce the risk of perinatal transmission;

- Counseling of women living with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce the risk of perinatal transmission of HIV;[16-18]

- Counseling of women living with HIV about the risks of HIV transmission through breast milk (breastfeeding is not recommended for women with HIV living in the United States);[19] *and*

- Early diagnostic evaluation of infants exposed to HIV (see Diagnosis of HIV Infection in Infants and Children), as well as testing of partners and other children, to permit prompt initiation of ART and any indicated prophylaxis.[1,20-22]

Technological improvements have resulted in an increased ability to detect early HIV infection and reduced performance time for laboratory-based assays; assays can now be completed in <1 hour. Accordingly, the Panels now incorporate CDC's 2014 Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations.[23] 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 HIV nucleic acid test (NAT) to establish diagnosis of acute HIV infection (see the CDC's Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens).

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, then 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 done 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)[24] for pregnant women with negative results on their initial HIV antibody tests who:[5]

- Are known to be at high risk of acquiring HIV (e.g., those who are injection drug users or partners of injection drug users, 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, or those who have been diagnosed with a new sexually transmitted disease during pregnancy. Additionally, an analysis of 2013 National HIV Behavioral Surveillance data found that the prevalence of risk-related sexual behaviors was higher in recently incarcerated women than in those who were never incarcerated);[25] *or*

- Are receiving health care in facilities in which prenatal screening identifies one or more pregnant woman with HIV per 1,000 women screened, or who reside in a jurisdiction that has a high incidence of HIV or AIDS in women between the ages of 15 and 45 years (a list of jurisdictions where such screening is recommended is found in the 2006 CDC recommendations; a more up-to-date list is forthcoming), or who reside in states that require third-trimester testing; *or*

- Have signs or symptoms of acute HIV (e.g., fever, lymphadenopathy, skin rash, myalgia, headaches, oral ulcers, leukopenia, thrombocytopenia, elevated transaminase levels).[2,26-28]

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. In these cases, an antigen/antibody combination immunoassay should be used, as these tests have a higher sensitivity in the setting of acute HIV infection than older antibody tests.[23,29] 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).

Providers should be proactive in assessing a woman's HIV acquisition risk and implementing third-trimester HIV retesting in areas where it is not routine, when indicated. A recent 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.[13,30] A study of data from 2007 to 2014 on Florida children 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, acute maternal infection (as indicated by negative results for initial tests). In addition, the study noted that third-trimester HIV tests were not performed in a portion of the patients.[30]

HIV Testing During Labor in Women with Unknown HIV Status

Women in labor whose HIV status is undocumented should undergo HIV testing in order 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

prophylaxis (see Intrapartum Antiretroviral Therapy/Prophylaxis) and in developing an appropriate ARV regimen for infants who are at high risk of perinatal transmission (see Table 11).[1-3,20,27,31,32]

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 women who receive an HIV diagnosis and their infants.

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.[23] Immediate initiation of maternal intravenous intrapartum zidovudine is recommended to prevent perinatal transmission of HIV pending the supplemental result after an initial positive expedited HIV test result (see Intrapartum Antiretroviral Therapy/Prophylaxis).[1-4,20,27] Pending results of supplemental maternal testing, infants should receive an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission as soon as possible, (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay, unless acute HIV infection is suspected.[23]

HIV Testing During the Postpartum Period

Women who have not been tested for HIV before or during labor should be offered expedited testing during the immediate postpartum period. When mothers are unavailable for testing, their newborns should undergo expedited HIV testing, using the antigen/antibody combination immunoassay.[1,20,27] 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 NAT test should be sent as well. Expedited HIV assays should be used to identify infants who have been exposed to HIV, because 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 mother or infant, it is strongly recommended that clinicians initiate an ARV regimen that is appropriate for infants who are at higher risk of perinatal HIV transmission and counsel the mother against breastfeeding. Both actions can be taken before the results of supplemental maternal HIV tests have confirmed the presence of HIV (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Breast milk can be expressed while supplemental HIV diagnostic testing is being completed, but it should not be given to the infant until testing confirms that the mother is HIV negative. 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.

Infant HIV Testing when Maternal HIV Test Results are Unavailable

When maternal HIV test results are unavailable (e.g., 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 is indicated to identify HIV in those infants or children.[1] Mechanisms should be developed to facilitate prompt HIV screening for infants who have been abandoned and are in the custody of the state. The choice of test will vary based on the age of the child (see Diagnosis of HIV Infection in Infants and Children).

Acute Maternal HIV Infection During Pregnancy or Breastfeeding

Women are more susceptible to HIV infection during pregnancy and the early postpartum period.[9] Risk of HIV exposure should be assessed in all women who are considering becoming pregnant, as well as in all pregnant women who previously tested HIV negative. Women with risk factors for HIV acquisition should receive prevention counseling and appropriate interventions, including pre-exposure prophylaxis if indicated (see Preconception Counseling and Care for Women of Childbearing Age Living with HIV). The risk of

perinatal transmission of HIV is increased in infants born to women who have acute HIV during pregnancy or lactation.[24,33-36] The antigen/antibody combination immunoassay will detect acute infection more quickly than other immunoassays, within approximately 10 days. 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 earlier than the antigen/antibody combination immunoassay. Women with possible acute HIV infection who are breastfeeding should cease breastfeeding immediately until HIV infection is confirmed or excluded.[19] Expressing breast milk can be recommended while HIV diagnostic testing is completed. Breastfeeding can resume if HIV infection is excluded and there is no ongoing maternal exposure to HIV. Care of pregnant or breastfeeding women 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 Women Living 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 persons 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 <mark>(Last updated December 14, 2018; last reviewed December 14, 2018)</mark>

Panel's Recommendations
• Virologic assays (i.e., HIV RNA and 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 tests should not be used **(AII)**.
• HIV RNA or HIV DNA <mark>NATs</mark> are generally equally recommended **(AII)**.
• <mark>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)**.</mark>
• Virologic diagnostic testing 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 at higher risk of perinatal HIV transmission, additional virologic diagnostic testing is recommended at birth **(AII)** and at 2 to 4 weeks after cessation of antiretroviral prophylaxis **(BII)**.
• A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.
• Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at age ≥1 month and one at age ≥4 months, or two negative HIV antibody tests from separate specimens obtained at age ≥6 months **(AII)**.
• Some experts confirm the absence of HIV at 12 to 18 months of age in children with prior negative virologic tests by performing an HIV antibody test to document loss of maternal HIV antibodies **(BIII)**.
• Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV NAT **(AII)**.
• Diagnostic testing in children with nonperinatal exposure only or children with perinatal exposure aged >24 months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV NAT may be necessary to diagnose HIV **(AII)**.
Note: The National Clinical 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*

<mark>Diagnosis of HIV Infection in Infants and Children</mark>

HIV can be definitively diagnosed through use of virologic assays in most non-breastfed infants with <mark>perinatal</mark> HIV exposure by age 1 month to 2 months, and in virtually all infants with HIV infection by age 4 months to 6 months. Antibody tests, including the newer 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. The first test result should be confirmed as soon as possible by a repeat virologic test on a second specimen, because false-positive results can occur with both RNA and DNA assays.[3] For additional

information on HIV and RNA assays and diagnosis of Group M non-subtype B and Group O HIV-1 infections and HIV-2 infections, see the relevant sections below.

Antigen/antibody combination immunoassays which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are not recommended for diagnosis of HIV in infants. The sensitivity of the antigen component in the first months of life is less than that of an HIV NAT, and antibody tests should not be used for diagnosis in infants and children <18 months of age.[4-6] 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 are HIV antibody-positive should be based on a NAT (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations). Diagnosis in children aged >24 months relies primarily on HIV antibody and antigen/antibody tests (see Diagnostic Testing in Children with Nonperinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months).[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 below[7] and receive antiretroviral (ARV) prophylaxis or empiric HIV therapy as soon as possible. For ARV management of HIV-exposed newborns and newborns with HIV infection (including those who do not yet have confirmed infection), see the Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV section.[8,9]

Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

Confirmation of HIV infection is based on the results of two positive virologic tests from separate blood samples in infants and children younger than 18 months. Figure 1 summarizes the timing of recommended virologic diagnostic testing for infants at low risk of transmission (based on maternal antiretroviral therapy [ART] and viral suppression) with additional time points to be considered for infants at higher risk and those on combination ARV prophylaxis regimens.

Figure 1. Recommended Virologic Testing Schedules for Infants Exposed to HIV by Perinatal HIV Transmission Risk

Low Risk: Infants born to mothers living with HIV who received standard ART during pregnancy and had sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) and no concerns related to maternal adherence.

Higher Risk: Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (during the late second or third trimester), received a diagnosis of acute HIV infection during pregnancy, or had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.
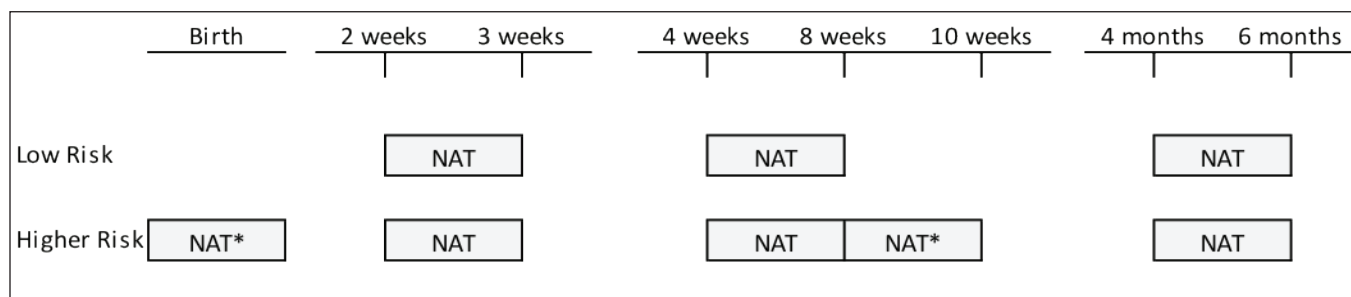
* For higher-risk infants, additional virologic diagnostic testing is recommended at birth and 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of life).

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

HIV infection can be **presumptively** excluded in nonbreastfed infants with two or more negative virologic tests (one at age ≥14 days 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.[1,7]

Definitive exclusion of HIV infection in a nonbreastfed 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 should not be breastfeeding. Many experts confirm the absence of HIV infection in infants with negative virologic tests by performing an antibody test at age 12 to 18 months to document seroreversion to HIV antibody-negative status.

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.[10] Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see the Pediatric Opportunistic Infection Guidelines and Initial Postnatal Management of the Neonate Exposed to HIV).

The case definition for **indeterminate** HIV infection status is an HIV-exposed child aged <18 months who was born to a woman living with HIV and who does not meet the criteria for having HIV infection or for having not contracted HIV. This includes infants who do not meet the minimum requirement for **presumptively** uninfected (e.g., having one negative test result at 4 weeks of age).

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

Virologic testing at birth should be considered for newborns who are at higher risk of perinatal HIV transmission,[11-16] such as infants born to women with HIV who:

- Did not receive prenatal care
- Did not receive antepartum or intrapartum ARV drugs
- Received intrapartum ARV drugs only
- Initiated ART late in pregnancy (late second or third trimester)
- Received a diagnosis of acute HIV infection during pregnancy
- Had detectable HIV viral load close to the time of delivery
- Received combination ARV drugs and did not have sustained viral suppression

Testing infants who have been exposed to HIV close to the time of birth only identifies 20% to 58% of infants with HIV infection. However, in one study that specifically evaluated infants born to mothers who had not received ARV drugs during pregnancy, and hence were at higher risk of *in utero* infection, birth testing identified 66.4% of infants with HIV infection.[17] Prompt diagnosis of infant HIV infection is critical to allow for discontinuing ARV prophylaxis and instituting early ART (see When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric ARV Guidelines). Blood samples from the umbilical cord should not be used for diagnostic evaluation because of the potential for contamination with maternal blood. Infants who have a positive virologic test result at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test result during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection.[11,12,18]

Virologic Testing at Age 14 to 21 Days

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,[7] and early identification of infection permits discontinuation of neonatal ARV prophylaxis and initiation of ART (see the Infants Younger than 12 Months section and Table 5 in When to Initiate Therapy in Antiretroviral-Naive Children in the Pediatric ARV Guidelines).

Virologic Testing at Age 1 to 2 Months

Testing performed at age 1 month to 2 months is intended to maximize the likelihood of detecting HIV infection in infants.[19,20] Two studies found that the type of maternal or infant prophylaxis used did not affect the sensitivity of diagnostic HIV testing. However, the sensitivity of diagnostic HIV testing was lower during the period of infant ARV prophylaxis than during the subsequent testing interval at 3 months of age, when the infant was no longer receiving prophylaxis. Overall, in both studies, 89% of infants with HIV infection were identified by 4 to 6 weeks of age. Repeat testing was performed at ≥4 to 6 weeks of age during the period of neonatal ARV prophylaxis on infants who had negative test results in the first 7 days of life. This repeat testing determined that 76% of those infants had HIV infection in one study[19] and 68% of those infants had HIV infection in the second study.[17] In both studies, all infants who had 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.

For infants at higher risk of perinatal HIV transmission, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission suggests an additional virologic test 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of age), given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis, may reduce the sensitivity of testing during prophylaxis.[7,17,19] In these situations, many experts recommend one test at age 4 weeks to 6 weeks to allow prompt recognition of infants with HIV, with an additional test at 8 weeks of life (2 weeks after cessation of prophylaxis at 6 weeks of life) to capture additional cases. For infants at low risk of 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 can be viewed as presumptively HIV uninfected, assuming the child has not had a positive prior virologic test result, laboratory evidence of CD4 immunosuppression, or clinical evidence indicative of HIV infection.

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, have no clinical evidence of HIV infection, and are not breastfed should be retested at age 4 to 6 months for definitive exclusion of HIV infection.

Antibody Testing at Age 6 Months and Older

Two or more negative results of HIV antibody tests that were performed in nonbreastfed infants at age ≥6 months can also be used to definitively exclude HIV infection in children with no clinical or virologic laboratory-documented evidence of HIV infection.[21,22]

Antibody Testing at Age 12 to 18 Months to Document Seroreversion

Some experts confirm the absence of HIV infection in infants and children with negative virologic test results (when there has not been prior confirmation of two negative antibody test results) by repeat serologic testing between 12 months and 18 months of age to confirm that maternal HIV antibodies transferred *in utero* have cleared.[1] In a study from 2012, the median age at seroreversion was 13.9 months.[23] Although the majority of infants who are without HIV will serorevert by age 15 months to 18 months, there are reports of late seroreversion after 18 months (see below). Factors that might influence the time to seroreversion include maternal disease stage and assay sensitivity.[23-26]

Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations

Late Seroreversion (≤24 Months of Age)

Nonbreastfed children with perinatal HIV exposure, no other HIV transmission risk, 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.[23-26] In one study, 14% of children with HIV exposure who were uninfected seroreverted after age 18 months.[23] These children may have had positive immunoassay results but supplemental antibody test results that indicated indeterminate HIV status (such as Western blot or immunofluorescence assay [IFA]). 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 definitively exclude or confirm HIV infection in children with perinatal HIV exposure, who continue to have a positive HIV antibody (or antigen/antibody) test at age 18 months to 24 months.

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 tests. This occurs in children who acquire HIV through an additional risk factor after completion of testing (see Diagnostic Testing in Children with Nonperinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months). If an HIV antibody test is positive at age 18 to 24 months, repeated virologic testing will distinguish late-seroreverting (uninfected) children with residual antibodies from children with antibodies due to underlying HIV infection.

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 and indeterminate HIV-1 Western blot results.[27-29] The diagnostic approach in these situations is discussed below in the sections on Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections and on Virologic Assays to Diagnose HIV-2 Infections.

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

Breastfeeding

Women with HIV should be encouraged to avoid breastfeeding (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Monitoring of infants born to women with HIV who opt to breastfeed should include immediate HIV diagnostic testing with a NAT and virologic HIV testing at the standard time points (see Figure 1 above). Many experts then recommend testing every 3 months throughout breastfeeding, followed by monitoring at 4 weeks to 6 weeks, 3 months, and 6 months after cessation of breastfeeding. Clinicians caring for a woman with HIV who is considering breastfeeding should consult with an expert and, if necessary, the Perinatal HIV Hotline (888-448-8765). See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed.[30-32]

Premastication

Receipt of solid food that has been premasticated or prewarmed (in the mouth) by a caregiver living with HIV is associated with risk of HIV transmission.[33-38] If this occurs in children with perinatal HIV exposure aged 24 months or younger with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing, as they may have residual maternal HIV antibodies (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations).

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. In such cases, maternal HIV status may be negative. If the maternal HIV status is unknown, age-appropriate testing should be performed as described for children with 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 cases of HIV transmission from these activities have been documented.[39]

Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with nonperinatal HIV exposure only or children with perinatal HIV exposure aged >24 months relies primarily on HIV antibody and antigen/antibody tests.[1,40] Food and Drug Administration (FDA)-approved diagnostic tests include:

- Antigen/antibody combination immunoassays, which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen. 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.[41]

- HIV-1/2 immunoassays (third-generation antibody tests) are alternatives for initial testing.

- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies is recommended for supplemental testing.

- HIV-1 NAT may be necessary as an additional test to diagnose acute HIV infection.

- HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests) are alternatives for supplemental testing, but will not detect acute HIV infection.

Diagnosis of HIV-2 in children with nonperinatal exposure or children with perinatal exposure aged >24 months relies on the Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories 2014 laboratory testing guidelines, which recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies for supplemental testing. This is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test; >60% of individuals with HIV-2 are misclassified as having HIV-1 by the HIV-1 Western blot.[1,42] 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 the CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is inconclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis, though this assay is not commercially available.[43,44]

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 1, 3, and 6 months of age and is comparable to HIV DNA PCR.[19] Results of quantitative assays that show HIV RNA levels <5,000 copies/mL may not be reproducible, and the test should be repeated before these results are interpreted as documentation of HIV infection in an infant.[45,46] Testing at birth will detect infants who acquire HIV *in utero* and not those who acquire HIV from exposure during or immediately prior to delivery (i.e., in 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 (similar to results of HIV DNA PCR for early diagnosis of HIV).[3,7,19,47]

HIV RNA undergoes reverse transcription to double-stranded DNA, which persists intracellularly within an infected cell. HIV DNA PCR assays detect intracellular DNA, and an individual receiving ART will continue to have a positive result even with a suppressed viral load. In contrast, HIV RNA assays are affected by

maternal antenatal treatment or infant combination ARV prophylaxis.[48] In one study, the sensitivity of HIV RNA assays were 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 infection receiving multidrug prophylaxis (n = 9) compared to levels among infants receiving single-drug zidovudine prophylaxis (n = 47) (median HIV RNA 2.5 $\log_{10}$ copies/mL vs. 5.4 log copies/mL, respectively). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log copies/mL) by age 3 months in both groups after stopping prophylaxis.[19] 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 regimens during those years, including Option A, Option B, and Option B+, as recommended by the World Health Organization.[49] Further studies are necessary to evaluate the sensitivity of HIV RNA assays in infants during receipt of three-drug ARV prophylaxis or empiric therapy.

An HIV quantitative RNA assay can be used as a supplemental test for infants who have an initial positive HIV DNA PCR test result. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared, and an HIV RNA measurement is available to assess baseline viral load. This viral load can also be used to determine HIV genotype and 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).

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.[18,50-53]

HIV DNA PCR and Related Assays

HIV DNA PCR is a sensitive technique 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 only detects *in utero* HIV infection and not infection in those infants who acquire HIV during the intrapartum period. This percentage increases to >90% by 2 weeks to 4 weeks of age and to 100% at ages 3 months and 6 months.[7,18,19,47]

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 (i.e., infants considered to have acquired HIV during the intrapartum period). A randomized, international study of 1,684 infants evaluated the efficacy of three different regimens of neonatal prophylaxis consisting of 6 weeks of zidovudine either alone or with two or three other ARV drugs; none of the infants' mothers had received prenatal ARV drugs. Infant testing was performed at birth, 10 to 14 days, 4 to 6 weeks, and 3 and 6 months (no testing was performed between 6 weeks and 3 months). Ninety-three of 140 infants (66.4%) with HIV infection were identified at birth, and by 4 to 6 weeks of age, 89% of the 140 infants were identified. Of the 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.[17] Data from Thailand showed that, in nonbreastfed infants, receiving a prophylaxis regimen of zidovudine/lamivudine/nevirapine for 6 weeks was associated with a delay in first HIV DNA detection. In this cohort, up to 20% of HIV-exposed infants had their first positive DNA PCR test after 2 months of age, prompting the authors to recommend infant testing at 4 months of age, after neonatal prophylaxis had been discontinued for at least 4 to 6 weeks.[54]

A recent study from Cape Town evaluated the sensitivity of HIV DNA assays within 8 days of life, during and after initiation of infant ART in infants with HIV. The infants had been exposed to a combination of maternal ART *in utero* and early ART for prophylaxis and treatment. The study noted that one infant subsequently had undetectable HIV DNA after 6 days on treatment, another was undetectable after 3 months, and a third was undetectable after 4 months. In seven infants who had 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 suggested that rapid decline of HIV-1 RNA and DNA may complicate definitive diagnosis.[55] A dataset of 38,043 infants from the Western Cape province of South Africa who were tested at a median age of 45 days of life in the setting of intensified vertical HIV transmission prevention regimens, particularly with the Option B+ program, showed that indeterminate PCRs decreased in frequency. These findings should be regarded with a high index of suspicion since many patients had positive results representative of true HIV infections on subsequent samples. These findings point out the need for additional virologic testing for definitive diagnosis.[56] Another group of South African investigators reported similar conclusions in a study of a cohort of 5,743 HIV-exposed neonates from Johannesburg.[57]

Although the AMPLICOR® HIV-1 DNA test has been widely used for diagnosis of infants born to mothers with HIV-1 infection since it was introduced in 1992, it is no longer commercially available in the United States. The sensitivity and specificity of noncommercial HIV-1 DNA tests (using individual laboratory reagents) may differ from the sensitivity and specificity of the FDA-approved commercial test.

The COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 qualitative test (which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots) may be used for infant diagnosis, but it is not approved by the FDA.[57-59]

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 are found in the United States with a widespread geographic distribution.[60] Recent data from the CDC National HIV Surveillance System showed that the number of foreign-born children with HIV has exceeded the number of U.S.-born children with HIV since 2011, with 65.5% of foreign-born children with HIV being born in sub-Saharan Africa and 14.3% in Eastern Europe.[61] In an evaluation of infants that 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.[62] Among a group of 40 children attending a pediatric HIV clinic in Rhode Island between 1991 and 2012, 14 (35%) acquired HIV with non-B HIV-1 subtypes. All 14 children with non-B subtypes were either born outside the United States or their parents were of foreign origin.[63] 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 non-B subtypes formed transmission clusters, including individuals with perinatally acquired infection.[64] In an analysis of 3,895 HIV-1 sequences collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms). Among individual states, the percentage of non-B subtypes ranged from 0% (in 12 states) to 28.6% in South Dakota, with seven states having percentages that were greater than 10%.[65]

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.[66] Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.[67-71] Geographical distribution of HIV groups is available at the HIV Sequence Database.

Currently available real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay have improved sensitivity for detection of non-subtype B HIV infection and the less common Group O strains, compared to older RNA assays that did not detect or appropriately amplify many non-B subtypes and Group O HIV[72-77] (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). Similarly, the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 qualitative test (a dual-target DNA/RNA test) can identify non-subtype B and Group O infections.[58,59]

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 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 a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody tests obtained at age ≥6 months provide further evidence to definitively rule out HIV infection. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or the CDC may be able to assist in obtaining referrals for diagnostic testing.

Virologic Assays to Diagnose HIV-2 Infections

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Cape Verde, Ivory Coast, the Gambia, Guinea-Bissau, Mali, Mauritania, Nigeria, Sierra Leone, Benin, Burkina Faso, Ghana, Guinea, Liberia, Niger, Nigeria, Sao Tome, Senegal, and Togo; and parts of India.[78-80] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.[81,82] HIV-1 and HIV-2 coinfections may also occur, but these are rare 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 developed to suppress HIV-1.[83-85]

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 a known or suspected HIV-2 infection. A mother should be suspected of having HIV-2 if her infection is linked to an area 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, repeatedly indeterminate results on HIV-1 Western blot, and HIV-1 RNA viral loads that are at or below the limit of detection; however, the current recommendation to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test).[1,86] 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.[43,44] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[78,87]

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Clinical and Laboratory Monitoring of Pediatric HIV Infection
(Last updated April 16, 2019; last reviewed April 16, 2019)

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 cell count is recommended for monitoring immune status in children 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 treatment-naive patients **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**.
• After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical adverse effects and should receive support for treatment adherence within 1 to 2 weeks, with laboratory testing for toxicity and viral load response recommended at 2 to 4 weeks after treatment initiation **(AIII)**.
• Children on ART should be monitored for therapy adherence, effectiveness, and toxicities routinely (every 3 to 4 months) **(AII*)**.
• Additional CD4 cell 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 cell count can be monitored less frequently (every 6 months–12 months) in children and adolescents who are adherent to therapy, who have CD4 cell count values that are well above the threshold for opportunistic infection risk and sustained virologic suppression, and who have had stable clinical status for more than 2 to 3 years **(AII)**. Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence and disease progression **(AIII)**.
• Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ART regimens **(BIII)**.
• The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, as mutations may not be detected once the drug has been discontinued. A history of all previously used ARV agents and available resistance test results must be reviewed when making decisions regarding the choice of new agents **(AII)**.
• Viral co-receptor (tropism) assays are recommended whenever a CCR5 antagonist is being considered for treatment **(AI*)**. The use of tropism assays should also 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) cell counts and plasma HIV RNA concentrations (viral loads) can vary significantly by age. The CD4 cell 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 Living With HIV

Initial Evaluation of Children Who Recently Received an HIV Diagnosis

Children who have recently received an HIV diagnosis should have their CD4 cell counts and plasma viral loads measured, and their growth and development should be evaluated for signs of HIV-associated abnormalities. They should also undergo a laboratory evaluation that looks for HIV-associated conditions,

including anemia, leukopenia, thrombocytopenia, hypoalbuminemia, nephropathy (urinalysis), and elevated levels of glucose, transaminases, or creatinine. In addition, children with HIV should have a complete, age-appropriate medical history and physical examination (see Table 3). 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).

Laboratory confirmation of HIV infection should be obtained if 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 is being considered as a component of the regimen, HLA-B*5701 testing should be sent prior to initiating abacavir, and an alternative ARV drug should be used if the HLA-B*5701 test result is positive (see the abacavir section in Appendix A: Pediatric Antiretroviral Drug Information).[1]

Before initiating therapy or making changes to a patient's regimen, a clinician should assess potential barriers to adherence and discuss the importance of adherence with the patient (see Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV).

If a child does not initiate ART after receiving an HIV diagnosis, the child's CD4 cell 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 patient's CD4 cell count and plasma viral load should be measured to establish a baseline for monitoring the patient's response to ART. To set the baseline for monitoring ART toxicity (see Management of Medication Toxicity or Intolerance), a complete blood count (CBC), urinalysis, and serum chemistry panel (including levels of electrolytes, creatinine, glucose, hepatic transaminases) should be performed. The levels of serum lipids (cholesterol, triglycerides) should also be measured. A CBC allows monitoring of zidovudine-associated anemia, leukopenia, and macrocytosis (see the zidovudine section in Appendix A: Pediatric Antiretroviral Drug Information). Electrolytes with anion gaps might help identify nucleoside reverse transcriptase inhibitor-associated lactic acidosis. In patients who are receiving tenofovir disoproxil fumarate, creatinine levels may increase, phosphate levels may decrease, and proteinuria can occur (see the tenofovir disoproxil fumarate section in Appendix A: Pediatric Antiretroviral Drug Information). Use of protease inhibitors may be associated with hyperglycemia. Levels of hepatic transaminases (alanine aminotransferase and aspartate aminotransferase) increase with the use of many ARV drugs. Bilirubin should be measured prior to starting atazanavir, because that drug causes an increase in indirect bilirubin (see the atazanavir section in Appendix A: Pediatric Antiretroviral Drug Information). For more information about the adverse effects (AEs) that are associated with a specific ARV drug, see Tables 15a-15k in Management of Medication Toxicity or Intolerance.

Clinical and Laboratory Monitoring After Initiating or Changing an Antiretroviral Therapy 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 should schedule frequent clinic visits and monitor patients closely during the first few months after initiating a new ART regimen. These visits are an opportunity for clinicians to provide support and discuss adherence with patients and their caregivers. The first few weeks of ART can be particularly difficult for children and their caregivers; they must adjust their schedules to allow for consistent and routine administration of medication doses. Children may also 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 visit to the clinician. It is critical that providers speak to caregivers and children in a supportive, nonjudgmental manner and use layman's terms. This promotes interactive reporting and ensures

that providers can have a productive dialogue with both children and their caregiver(s), even in situations where medication adherence is reported to be inconsistent.

Within 1 to 2 Weeks of Initiation of Antiretroviral Therapy

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

2 to 4 Weeks after Initiation of Antiretroviral Therapy

Most experts recommend performing laboratory testing at 2 weeks to 4 weeks (and not >8 weeks) after initiation of ART to assess virologic response and laboratory toxicity, though this recommendation is based on limited data. The laboratory chemistry tests that a patient requires will depend on the regimen the patient is receiving (see above). 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 after 4 weeks to 8 weeks of ART.

Clinical and Laboratory Monitoring for Children who are Stable on Long-Term Antiretroviral Therapy

After the initial phase of ART initiation (1 month–3 months), clinicians should assess a patient's adherence to the regimen and the regimen's effectiveness (as measured by CD4 cell count and plasma viral load) every 3 months to 4 months. Additionally, clinicians should review a patient's history of toxicities and evaluate a 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 3 provides one proposed general monitoring schedule, which should be adjusted based on the specific ART regimen a child is receiving.

A patient's baseline CD4 cell count affects how rapidly CD4 cell count improves after ART initiation; children with very low CD4 cell counts may take longer than 1 year to achieve their highest values after viral load suppression.[2]

Recent studies have critically evaluated the frequency of laboratory monitoring in both adults and children, particularly CD4 cell count and plasma viral load. These studies support less frequent monitoring in stable patients who have been consistently virologically suppressed for ≥1 year.[3-9]

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

- Consistent virologic suppression for longer than 2 years

- CD4 cell counts 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 cell count less frequently (e.g., every 6 months to 12 months) in children and adolescents who are adherent to therapy, who have CD4 cell count values well above the threshold for OI risk, and who have had sustained virologic suppression and stable clinical status for >2 years to 3 years.[10] Some clinicians find value in scheduling visits every 3 months even when lab testing is not performed, in order to review adherence and update drug doses for interim growth.

Testing at the Time of Switching Antiretroviral Therapy

When a patient switches regimens in order 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 of ART failure (see Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy), 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 the use of 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 ART regimens.[11]

Immunologic Monitoring in Children: General Considerations

When interpreting CD4 cell counts and percentages in children, clinicians must consider age as a factor. CD4 cell 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 HPPM Collaborative Study found that CD4 percentage provided little or no additional prognostic value compared with CD4 cell count regarding short-term disease progression in children aged <5 years; similar results were reported in a study of older children.[12] The current pediatric HIV disease classification is based on absolute CD4 cell count, which is the preferred assay for monitoring and estimating the risk for disease progression and OIs.[13]

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

Medical practice guidelines now recommend that all people with HIV receive ART, regardless of their CD4 cell count and clinical stage. However, CD4 cell counts are used to determine risk profiles that affect the urgency of recommendations for when to initiate therapy in a treatment-naive child with HIV infection and when to assess the need for OI prophylaxis (see When to Initiate). 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 cell count or HIV RNA viral load measurement.[14]

CD4 cell counts and percentages can show considerable intrapatient variation.[15] Mild intercurrent illness, the receipt of vaccinations, or exercise can produce a transient decrease in CD4 cell count and percentage; thus, CD4 cell 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 cell count or percentage in conjunction with a confirmed viral load determination. The CD4 cell count/percentage and viral load measurement should be confirmed by performing the test a second time at least 1 week after the first test.

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 high peak levels during the period of primary infection in adults and adolescents, and then it declines by as much as 2 to 3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6 months to 12 months after acute infection.[16,17] In adults with HIV, the stable lower level (or virologic set point) correlates with the subsequent risk of disease progression or death in the absence of therapy.[18]

The pattern of change in plasma viral load in untreated infants with perinatal HIV infection differs from that in adults and adolescents with HIV infection. High plasma viral loads persist in untreated children for prolonged periods.[19,20] 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.[21] After the first year of life, plasma viral load slowly declined during the next few years.[21-24] Viral load during the first 12 months 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 years 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.[25]

Despite the established association between high plasma viral load and disease progression, a specific HIV RNA concentration has only moderate predicative value for disease progression and death in an individual child.[23] 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.[20] In both children and adults with HIV, CD4 cell count or percentage and plasma viral load are independent predictors of disease progression and mortality risk, and using the two markers together more accurately defines prognosis.[23,24,26,27]

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 detection 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).[28] Temporary viral load elevations ("blips") that are between the level of detection and 500 copies/mL often are detected in adults[29] and children who are on ART; 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 in Management of Children Receiving Antiretroviral Therapy. 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 4). 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 or more.[30,31] 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.[32-34]

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 is important for many regions of the world where non-B subtypes are predominant, as well as for the United States, where a small subset of individuals contract non-B viral subtypes.[32,35-39] It is particularly relevant for children who are born outside the United States or to foreign-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 in either direction during the course of a day or on different days.[26,31] 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 in infants aged <2 years and differences >0.5 $\log_{10}$ copies/mL 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. Clinicians should consult an expert in pediatric HIV infection when making clinical decisions based on plasma viral loads, due to the complexities of HIV RNA testing and the age-related changes in plasma viral load in children.

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's 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.[40,41] In addition, some human genetic polymorphisms are associated with drug toxicity or adverse events (e.g., using HLA-B*5701 testing to predict abacavir hypersensitivity; for more information, see the abacavir section of the drug appendix).[42] Future clinical practice is likely to feature broader applications of multiple forms of genetic testing to guide management of health and disease.

Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (page 1 of 2)

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]	When Switching ARV Regimens
Medical History and Physical Examination	√	√	√	√	√	√		√
Adherence Evaluation		√	√	√	√	√		√
CD4 Count	√	√	√			√		√
Plasma Viral Load	√	√	√		√	√		√
Resistance Testing	√							√
CBC with Differential	√	√	√		√	√		√
Chemistries[f]	√	√	√		√	√		√
Lipid Panel	√		√				√	
Random Plasma Glucose[g]			√				√	
Urinalysis	√		√				√	
Hepatitis B Screening[h]		√						√
Pregnancy Test for Women of Childbearing Age[i]		√						√

Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy (page 1 of 2)

[a] See text for details on recommended laboratory tests to perform.

[b] A patient's ability to adhere to an ARV regimen is assessed prior to starting ART. If abacavir is being considered as part of the regimen, send HLA-B*5701 testing prior to initiating abacavir 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 that is associated with a patient's ART regimen and the patient's medical history (see text).

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

[d] CD4 cell count, CBC, and chemistries can be monitored less frequently (every 6 months–12 months) in children and youth who are adherent to therapy, who have CD4 cell values that are well above the threshold for OI risk, and who have had sustained virologic suppression and stable clinical status for more than 2 years 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 might be needed. For patients treated with TDF, more frequent urinalysis should be considered.

[f] Chemistries refer to a comprehensive metabolic panel.

[g] Random plasma glucose is collected in a gray-top blood collection tube or other designated tube.

[h] This screening is only recommended for individuals who have previously demonstrated no immunity to hepatitis B and who are initiating a regimen that contains ARV drugs with activity against hepatitis B, specifically lamivudine, emtricitabine, TAF, or TDF.

[i] See the Adult and Adolescent Antiretroviral Guidelines, as well as Preconception Counseling and Care for Women of Childbearing Age Living with HIV in the Perinatal Guidelines.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; CBC = complete blood count; CD4 = CD4 T lymphocyte; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; OI = opportunistic infection

Table 4. 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
Method	Real-time RT-PCR	Real-time NASBA	Real-time RT-PCR	Real-time RT-PCR
Dynamic Range	$40–10^7$ copies/mL	$25–10^7$ copies/mL	$20–10^7$ copies/mL	$37–11\times10^7$ copies/mL
Specimen Volume[a]	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL
Manufacturer	Abbott	bioMerieux	Roche	Siemens

[a] Smaller volumes for children can be accommodated.

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

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Treatment Recommendations

General Considerations

Since the introduction of potent combination antiretroviral (ARV) drug regimens in the mid-1990s, the treatment of pediatric HIV has steadily improved. These potent regimens have the ability to suppress viral replication, thus lowering the risk of virologic failure due to the development of drug resistance. Antiretroviral therapy (ART) that includes at least three drugs from at least two drug classes is recommended; such regimens have been associated with enhanced survival, reduced incidence of opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children.[1-4] In the United States and the United Kingdom, significant declines in morbidity, mortality, and hospitalizations have been reported in children living with HIV between 1994 and 2006, concomitant with increased use of highly active combination regimens. The goal of treatment is to optimize immune status and general health to ensure a full and productive adult life.[5-7] As a result, individuals with perinatally acquired HIV infection are now living well into adulthood.

It can be challenging to select successive new ARV drug regimens across the lifetime of a child with perinatally acquired HIV. In addition, therapy is associated with short-term and long-term toxicities, which can be recognized in childhood or adolescence (see Management of Medication Toxicity or Intolerance).[8-12]

Drug-resistant virus can develop during ART when viral replication occurs in the presence of subtherapeutic ARV concentrations, which can be caused by poor adherence, poor absorption, a regimen that is not sufficiently potent, or a combination of these factors. In addition, primary drug resistance may be seen in ARV-naive children who have contracted a resistant virus.[13-17] Thus, clinicians must consider a number of factors when deciding which drugs to choose for ARV-naive children (see What to Start) and how to best treat ARV-experienced children remains complex.

Decisions regarding the management of pediatric HIV should be directed by or made in consultation with a specialist in pediatric HIV infection whenever possible. Treatment of ARV-naive children (including information on when to start treatment and which drugs to use), when to change therapy, and treatment of ARV-experienced children are discussed in separate sections of the guidelines. For guidance about treatment of sexually mature adolescents, see the Adult and Adolescent Antiretroviral Guidelines.

In addition to trials that have demonstrated the benefits of ART in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,[18] a randomized clinical trial has provided evidence that initiating ART in asymptomatic adults with CD4 cell counts >500 cells/mm^3 is beneficial as well.[19] Similarly, improved outcomes have been shown with initiation of ART in asymptomatic infants aged 6 weeks to 12 weeks.[20] Although there are fewer available data on the risks and benefits of immediate therapy in asymptomatic children with HIV than in adults, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends ART for all children with HIV (see When to Initiate Therapy in Antiretroviral-Naive Children).

Several factors need to be considered when making decisions about the urgency of initiating and changing ART in children, including:

- Age (see When to Initiate Therapy in Antiretroviral-Naive Children); *and*

- Severity of HIV disease and risk of disease progression, as determined by the presence of HIV-related illnesses (see When to Initiate Therapy in Antiretroviral-Naive Children) or a history of HIV-related illnesses, and the patient's degree of CD4 immunosuppression (see Revised Surveillance Case Definition for HIV Infection).

General considerations for choosing specific ARV drugs for ART include (see What to Start):

- Presence of drug-resistant virus;

- Availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child's age/weight group;

- Potency, complexity (e.g., dosing frequency, food requirements), and potential short-term and long-term adverse effects of the ART regimen;

- Effect of initial regimen choice on later therapeutic options;

- A child's ART history;

- Presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect decisions about drug choice and the timing of therapy initiation;

- Potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a child; *and*

- The anticipated ability of the caregiver and child to adhere to the regimen.

The following recommendations provide general guidance for treating children who are living with HIV, but a child's individual circumstances should be considered when making treatment decisions. Guidelines for the treatment of children living with HIV are evolving as new data from clinical trials become available. Although prospective, randomized, controlled clinical trials offer the best evidence for creating guidelines, most ARV drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting PK and safety data from Phase 1/2 trials in children. In addition, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Panel reviewed relevant clinical trials that were published in peer-reviewed journals or in abstract form, with attention to data from pediatric populations when available.

Goals of Antiretroviral Treatment

Currently available ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV, due to the persistence of HIV in CD4 cells and other long-lived cells.[21-23] In one case, a child with HIV who was treated with ART between 30 hours and 18 months of age achieved more than 2 years of undetectable HIV RNA levels while off ART. However, the child subsequently experienced viremic rebound.[24,25] There are data to suggest that, after viral suppression, the mean half-life of intracellular HIV proviral DNA can be up to almost 16 years.[26] Thus, based on currently available data, HIV causes a chronic infection that likely requires life-long treatment once a child starts therapy. The goals of ART for children living with HIV include:

- Preventing and reducing HIV-related morbidity and mortality;

- Restoring and/or preserving immune function, as reflected by CD4 cell counts;

- Maximally and durably suppressing viral replication;

- Preventing emergence of viral drug-resistance mutations;

- Minimizing drug-related toxicity;

- Optimizing growth, sexual maturation, and neurocognitive development;

- Improving quality of life; *and*

- Preventing transmission of HIV to others

Strategies to achieve these goals require a complex balance of potentially competing considerations.

Selection of an Antiretroviral Therapy Regimen

The treatment of choice for children with HIV is a regimen that contains at least three drugs from at least two classes of ARV drugs. The Panel has recommended several *Preferred* and *Alternative* regimens (see What to Start). The most appropriate regimen for an individual child depends on multiple factors, as noted above. A regimen that is characterized as an *Alternative* in the guidelines may be a preferred regimen for some patients.

Drug Sequencing and Preservation of Future Treatment Options

When choosing an ART regimen, clinicians should consider the need for future treatment options and take into account the presence of or potential for drug resistance. Making multiple changes to an ART regimen can rapidly exhaust treatment options and should be avoided. Choosing an appropriate sequence of drugs for initial and second-line therapy can preserve future treatment options and can help maximize long-term benefit from therapy. The current recommended regimens for initial therapy include two classes of drugs (see What to Start), thereby sparing three classes of drugs for later use.

Maximizing Adherence

As discussed in Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV, poor adherence to prescribed regimens can lead to subtherapeutic concentrations of ARV medications, which increases the risk of developing drug resistance and the likelihood of virologic failure. Outside of the very young age group (aged <1 year) and children with significant immunologic impairment or clinical HIV symptoms (therapy should be initiated within 1–2 weeks of diagnosis in these children, with an expedited discussion on adherence and close follow-up), the risk of rapid disease progression is low. This provides adequate time to fully assess, identify, discuss, and address issues associated with potential adherence problems with the caregivers and the child (when age-appropriate) prior to initiating therapy. Participation by the caregiver and child in the decision-making process is crucial. In addition, frequent follow-up is important to assess virologic response to therapy, drug intolerance, viral resistance, and adherence. Finally, in patients who experience virologic failure, it is critical to fully assess adherence and possible viral resistance and to consider measuring serum drug concentrations before making changes to the ART regimen.

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When to Initiate Therapy in Antiretroviral-Naive Children <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

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Panel's Recommendations

- Antiretroviral therapy (ART) should be initiated in all antiretroviral-naive infants and children with HIV infection (**AI**, **AI*** or **AII**; see Table A for details**)**.
  - Rapid ART initiation (within 1-2 weeks of diagnosis) including an expedited discussion of adherence is recommended for all children <12 months and those with CDC Stage 3-defining conditions.
  - In other situations, sufficient time to fully assess and address issues associated with adherence should be allowed prior to ART initiation.
- Every 3 to 4 months, health care providers should closely monitor the virologic, immunologic, and clinical status of any child with HIV who has not initiated ART (**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*

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Overview

The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiating antiretroviral therapy (ART) in all adults and adolescents with HIV (see the Adult and Adolescent Antiretroviral Guidelines). In addition to trials demonstrating the benefits of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,[1] a randomized clinical trial has shown definitive benefits to initiating ART in asymptomatic adults with CD4 cell counts >500 cells/mm^{3}. The START trial randomized 4,685 antiretroviral (ARV)-naive adults with HIV (median age: 36 years) who had CD4 cell counts >500 cells/mm^{3} to immediately initiate ART or to defer ART until their CD4 cell counts declined to <350 cells/mm^{3} or until they developed any condition that dictated the use of ART. Forty-two patients in the early treatment group met the primary composite endpoint for the study (which included AIDS, serious non-AIDS events, or death) compared with 96 patients who met the primary endpoint in the deferred treatment group, for an overall 57% reduction in risk of serious illness or death with early treatment (*P* < 0.001). It should be noted that the absolute risk for meeting the primary endpoint was low: 3.7% of patients in the deferred arm versus 1.8% of patients in the immediate treatment arm. Sixty-eight percent of the primary endpoints occurred in patients with CD4 cell counts >500 cells/mm^{3}. The risks of Grade 4 events or unscheduled hospital admissions were similar between the two groups.[2]

A second analysis of the data from this study provided additional support for immediate ART initiation. Complementing the original intention-to-treat analysis, a per-protocol analysis showed that 30% of participants assigned to deferred initiation actually started ART earlier than specified by the protocol, so that the per-protocol risk of serious illness or death was 66% lower with immediate ART (or the benefit was 23% greater) than suggested by the intention-to-treat analysis.[3] Finally, when quality of life was assessed in START Trial participants using validated self-assessment tools, there were modest but significant improvements in reported quality of life among those who immediately initiated treatment versus those who deferred ART.[4] The recommendation to initiate therapy in all adults and adolescents with HIV is also based on the availability of effective ART regimens that are well tolerated, as well as evidence that effective ART reduces secondary sexual HIV transmission.[5]

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) also recommends initiating treatment for all children with HIV, <mark>as do the European pediatric HIV experts in</mark>

the 2016 Pediatric European Network for Treatment of AIDS Treatment Guidelines.[6] However, the urgency for immediate initiation varies by age and pretreatment CD4 cell count, due to less available data regarding benefits and risks of immediate therapy in asymptomatic children with HIV than in adults. Concerns about adherence and toxicities become particularly important when therapy is initiated at an early age and will likely continue throughout the patient's life. In children aged <1 year, the health and survival benefit of immediate ART initiation has been clearly demonstrated in the CHER trial.[7] In addition, Shiau et al. reported that, in a study of two cohorts of infants with HIV in Johannesburg, South Africa, infants who initiated ART at ages <6 months had better sustained viral control after achieving suppression than infants who started therapy between the ages of 6 months and 24 months.[8] Several studies have identified that treatment initiation within the first year of life is also associated with reduced size of viral reservoirs.[9-12] Data in older children are equivocal. The PREDICT trial, which enrolled children aged 1 year to 12 years (median age: 6.4 years), found that the risk of clinical progression was extremely low in both children receiving immediate ART and children receiving delayed ART (initiation was determined by CD4 cell count); additionally, no clinical benefit of immediate ART was observed.[13] In contrast, in an observational study that included more than 20,000 children aged 1 year to 16 years from 19 cohorts in Europe, Southern Africa, and West Africa, immediate ART was associated with lower mortality and better growth in children aged <10 years when compared with ART that was delayed until CD4 cell count decreased to <350 cells/mm^3. In children aged >10 years at enrollment, immediate ART initiation had no observable effect on mortality or growth.[14]

Rapid initiation of therapy, defined as therapy that is initiated within 1 or 2 weeks of diagnosis, in the early stages of HIV infection in both children and adults could potentially control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species. Initiation of therapy at higher CD4 cell counts has been associated with the presence of fewer drug-resistance mutations at virologic failure in adults.[15] Early therapy also preserves immune function, preventing clinical disease progression.[16,17] Ongoing viral replication may be associated with persistent inflammation and the development of cardiovascular, kidney, and liver disease and malignancy; studies in adults also suggest that early control of replication may reduce the risk of these non-AIDS complications.[16,18-20]

Table A. Treatment Recommendations for Initiation of Antiretroviral Therapy in Antiretroviral-Naive Infants and Children with HIV

Age	Criteria	Recommendation
<12 Months[a]	Regardless of clinical symptoms, immune status, or viral load	Rapid initiation[b] of treatment (**AII**, but **AI** for children aged ≥6 weeks to <12 weeks)
1 Year to <6 Years	CDC Stage 3-defining conditions[c]	Rapid initiation[b] of treatment (**AI***)
	CDC Stage 3 immunodeficiency:[d] CD4 cell count <500 cells/mm³	
	Moderate HIV-related symptoms[c]	Treat[e] (**AII**)
	CD4 cell count[c] 500–999 cells/mm³	
	Asymptomatic or mild symptoms[c] **and** CD4 cell count[c] ≥1,000 cells/mm³	Treat[e,f] (**AI***)
≥6 Years[g]	CDC Stage 3-defining conditions[c]	Rapid initiation[b,] of treatment (**AI***)
	CDC Stage 3 immunodeficiency:[d] CD4 cell count <200 cells/mm³	
	Moderate HIV-related symptoms[c]	Treat[e] (**AII**)
	CD4 cell count[d] 200–499 cells/mm³	
	Asymptomatic or mild symptoms[c] **and** CD4 cell count ≥500 cells/mm³	Treat[e,f,g] (**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 and adolescents but not studies limited to post-pubertal adolescents

[a] Treatment of infants aged ≤2 weeks is complex, and it is an area of active investigation. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.

[b] Within 1 week–2 weeks, including an expedited discussion on adherence.

[c] See Table 6 for definitions.

[d] CD4 cell counts should be confirmed with a second test to meet the treatment criteria before initiating ART.

[e] Allow sufficient time to fully assess and address issues associated with adherence prior to initiating therapy.

[f] Patients and caregivers, together with their health care providers, may (on a case-by-case basis) decide to defer therapy due to clinical and/or psychosocial factors. Patients should be monitored closely in these cases.

[g] For adolescents aged ≥13 years with SMRs of 4 or 5, see the Adult and Adolescent Antiretroviral Guidelines.

Note: Potential barriers to adherence should be assessed and discussed with children who have HIV and their caregivers before initiation of therapy (**AIII**).

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; SMR = sexual maturity rating

Infants Younger Than 12 Months

The CHER trial was a randomized clinical trial in South Africa that initiated triple-drug ART in asymptomatic infants aged 6 weeks to 12 weeks who had 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.[7] Most of the infant deaths in the delayed treatment arm occurred during the first 6 months after study entry. A substudy of this trial also found that infants who were treated early had significantly better gross motor and neurodevelopmental profiles than those who had their therapy deferred.[21] In a study conducted among

Kenyan infants with HIV who initiated treatment before 6 months of age and who were on treatment for at least 6 months, infants with an effective response to treatment, defined as HIV viral suppression <1,000 copies/mL, CD4 percentages ≥25%, and weight-for-age z-scores ≥-2 at 9 months of age, had better gross motor and language attainment than infants who did not meet the parameters for effective treatment response. These findings highlight the importance of early, efficacious treatment.[22]

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.[23] Shiau et al. reported that, 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 therapy between 6 months and 24 months.[8] A 2011 surveillance study followed infants who had recently received a diagnosis of HIV and who were aged <24 months (N = 272, median age: 6.1 months) from five inpatient or outpatient settings in Johannesburg, South Africa. By 6 months post-enrollment, 53 infants (19.5%) had died and 73 infants (27%) were lost to follow-up. Despite these discouraging results, there was a 71% reduction in the 6-month risk of death among the children who initiated ART, and infants identified through routine prevention of perinatal transmission or immunization clinics were five times less likely to die than those who received an HIV diagnosis during a symptomatic hospital admission.[8,24]

Finally, several studies have reported that early treatment of infants with perinatally acquired HIV is also associated with reduced size of viral reservoirs.[9-12] Kuhn et al. found that initiating ART at a younger age was associated with lower levels of peripheral blood mononuclear cell (PBMC)-associated HIV DNA. Furthermore, the authors reported that the risk of viral rebound to >50 copies/mL was two-fold higher (P = 0.0006) in the first 36 months after treatment initiation for infants with HIV DNA reservoir levels >55 copies/10^6 cells than for infants with HIV DNA reservoir levels ≤55 copies/10^6 cells.[10] This finding may indicate that initiating treatment 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 likely event for infants destined for life-long treatment.

Given the risk of rapid HIV disease progression and mortality in young infants, and taking into account the findings from multiple studies, including the CHER trial, that demonstrate immune, growth, and neurodevelopmental benefits associated with early treatment initiation among infants with perinatally acquired HIV, the Panel recommends rapid initiation of therapy (within 1 week–2 weeks) for all infants aged <12 months, regardless of clinical status, CD4 percentage, or viral load. Before therapy is initiated, it is important to assess and discuss issues associated with adherence with an infant's caregivers. However, given the high risk of disease progression and mortality in young infants with HIV, it is important to expedite this assessment in infants aged <12 months, and provide intensive follow-up during the first few weeks to months to support the caregiver. The risk of disease progression is inversely correlated with the age of a child, with the youngest infants at the greatest risk of rapid disease progression. Progression to moderate or severe immune suppression also occurs frequently in older, untreated infants with HIV; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[25] In the HPPMC study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger children than in older children at any given CD4 percentage, particularly for infants younger than 12 months.[26] Furthermore, clinical and laboratory parameters are limited in their ability to determine which young infants are at risk of rapid disease progression. No specific "at-risk" viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections (OIs) can occur in young infants with normal CD4 cell counts.[26]

Identifying HIV infection during the first few months of life permits clinicians to initiate ART during the initial phases of primary infection. Consistent with the CHER trial, data from a number of observational studies in the United States and Europe demonstrate that infants who receive early treatment are less likely to progress to AIDS or death, and they have improved growth compared to those who start therapy later.[16,27-29]

Several small studies have demonstrated that, despite the very high levels of viral replication in infants with perinatally acquired HIV, initiating treatment early can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.[30,31] In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests that near-complete control of viral replication can be achieved.[32,33] Early initiation of suppressive ART (i.e., in infants aged <6 months) results in a significant proportion of infants with HIV who clear maternally-acquired antibodies to HIV but who fail to produce their own HIV-specific antibody. These infants appear to be HIV seronegative when tested; however, viral reservoirs remain, and viral rebound will occur if ART is stopped.[32,34-37] Although there are a limited number of case reports of lengthy remissions in children with perinatally acquired HIV, current ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV because HIV persists in CD4 cells and other long-lived cells.[38-42] For these reasons, the Panel **does not recommend** empiric treatment interruption.

The report of a prolonged remission in a child with perinatally acquired HIV in Mississippi generated discussion about early initiation of ART in newborn infants with high-risk HIV exposure. This newborn, born to a mother who did not receive antenatal or perinatal ART, was treated with a three-drug ART regimen at age 30 hours through age 18 months. ART was then discontinued against medical advice. Intensive follow-up evaluations showed no evidence of virologic rebound following discontinuation of ART until age 46 months (27 months after the discontinuation of ART), when the plasma viral load rebounded to 16,750 copies/mL; this viral load was confirmed with repeat testing. ART was restarted at that time.[43,44] This experience has prompted increasing support for initiation of treatment during the first weeks of life, as soon as the diagnosis is made. However, managing neonates with HIV is complex from both a medical and social perspective. Because of limited safety and pharmacokinetic data and limited experience with the use of ARV drugs in infants aged <2 weeks to 4 weeks, particularly among premature infants, drug and dose selection in this age group is challenging (see What to Start and Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV).[45] In a single-center, retrospective review of 22 infants with HIV who started ART during the first month of life (median age at initiation: 13.5 days) in Cape Town, South Africa, only half remained in care at a mean age of 2.1 years, and only two had viral suppression <50 copies/mL when last measured.[46]

Virologic suppression may take longer to achieve in young children than in older children or adults.[47-49] Possible reasons for the slower response in infants include higher virologic set points in young infants, inadequate ARV drug concentrations, and poor adherence because of the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70% to 80% have been reported in infants with HIV who initiated therapy at ages of <12 months.[16,50,51] In a 5-year follow-up study of 40 children with HIV who initiated treatment at ages of <6 months, 98% had CD4 percentages >25% and 78% had undetectable viral load with a median follow-up time of 5.96 years.[16]

More rapid viral suppression in young infants may help reduce the size of long-lived HIV reservoirs. Several studies that compared the size of the viral reservoirs in children who initiated ART before age 12 weeks to those who initiated ART at age 12 weeks to 1 to 2 years have found that the size of the viral reservoir (as measured by 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.[52-54] Similarly, in a cross-sectional substudy of 144 youth with perinatally acquired HIV and long-term viral suppression in the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, a lower proviral reservoir was found in those who achieved virologic control at <1 year of age than in those who achieved virologic control at 1 to 5 years of age or >5 years of age (4.2 vs. 19.4 vs. 70.7 copies/million PBMCs, respectively).[55] In addition, among 61 children with perinatally acquired HIV in PHACS who achieved viral suppression at ages of <1 year versus ages between 1 year and 5 years, the mean half-life of HIV DNA from viral suppression was shorter in the early suppressors—5.9 years versus 18.8 years, respectively.[56]

Information on the appropriate drug doses for infants aged <3 months, and particularly preterm infants, is limited.[45] Hepatic and renal functions are immature in newborns, who are undergoing rapid maturational changes during the first few months of life. This can result in substantial differences in ARV dose

requirements between young infants and older children.[57] When drug concentrations are sub-therapeutic, 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).

Finally, the possibility of long-term toxicities (e.g., lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, mitochondrial dysfunction) with prolonged therapy is a concern.[58] However, early initiation of ART reduces mortality and morbidity in infants, and this benefit outweighs such potential risks.

Children Aged 1 Year and Older

In general, disease progression is less rapid in children aged ≥1 year.[25] However, children with Centers for Disease Control and Prevention (CDC) Clinical Stage 3-defining OIs (see Revised Surveillance Case Definition for HIV Infection and Table 6) are at high risk of disease progression and death. The Panel recommends rapid treatment initiation (i.e., initiation within 1 week–2 weeks) for all such children with severe HIV disease, regardless of immunologic or virologic status. In these cases, the clinical team should expedite a discussion on adherence and provide intensive follow-up during the first few weeks to months to support the children and families. Children aged ≥1 year who have mild to moderate clinical symptoms (see Table 6) or who are asymptomatic are at lower risk of disease progression than children with more severe clinical symptoms.[59] ART is also recommended for these children, but because the risk of rapid disease progression is lower, more time can be taken to fully assess, discuss, and address issues associated with adherence with the caregivers and children prior to initiating therapy.

The Cochrane Collaboration[60] published a review on the effectiveness of ART in children with HIV aged <2 years based on data from published, randomized trials of early ART versus deferred ART.[7,61] The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that these benefits were less pronounced in infants who started ART between ages 1 year and 2 years.

The PREDICT multicenter, open-label 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%.[62] AIDS-free survival at 144 weeks was 98.7% (95% confidence interval [CI], 94.7% to 99.7%) in the deferred group and 97.9% (95% CI, 93.7% to 99.3%) in the immediate therapy group ($P = 0.6$). However, because of the low event rate, the study was underpowered to detect a difference between the two groups. Neurodevelopmental outcomes were similar with immediate versus deferred ART initiation, but both groups performed worse than the children without HIV.[13] The trial did show better height gain for children who started ART immediately.[62] This study likely had a selection bias toward individuals with relatively slowly progressing disease, because it enrolled children who had survived a median of 6 years without ART. The low enrollment of children aged <3 years limits its value in making recommendations in that age group.

A retrospective analysis of 245 Brazilian children with perinatally acquired HIV who initiated ART between 2002 and 2014 at a median of 52 months of age (interquartile range: 18–94 months) found that there was no statistical difference between mortality among children who initiated ART at <18 months of age (7.9%) and those who initiated ART after developing symptoms or reaching an age >18 months (12.4%). However, because the median age of the late presenters was approximately 5 years, the results do not take into consideration children with rapidly progressing disease who may have died prior to HIV diagnosis; those who presented later may have been slow progressors with a better prognosis.[63]

In contrast, 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.[14] In children aged <10 years at enrollment,

there was lower mortality and higher mean height-for-age z-score after 5 years of follow-up among participants who initiated ART immediately than among those who delayed treatment until their CD4 cell counts decreased to <350 cells/mm^3. The best outcomes were observed in European children, who attained growth outcomes comparable to those of children without HIV. However, immediate ART initiation produced no observable benefits or risks in those aged >10 years at enrollment.

Available data suggest that both children and adults who initiate treatment with a higher CD4 percentage or CD4 cell count have better immune recovery than patients who initiate with lower CD4 percentages or CD4 cell counts.[64-68] In the PENPACT-1 clinical trial, >90% of children recovered a normal CD4 cell count when ART was initiated during "mild" immunosuppression at any age, or during "advanced" immunosuppression at <3 years of age. Observational studies in children have reported similar findings. Among 1,236 children with perinatally acquired HIV in the United States, only 36% of those who started treatment 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%.[69] Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.[29,30,69,70]

Additionally, U.S. and international studies have reported that delaying ART initiation until later in childhood adversely impacts growth and substantially delays pubertal development and menarche, independent of immune suppression.[71-73] Finally, the PREDICT study demonstrated that patients in the early treatment arm had improved height-for-age z-scores compared with the patients in the deferred arm, who showed no improvement.[62] These combined data suggest that initiation of ART at higher CD4 values and younger ages maximizes the potential benefit for immunologic recovery and optimizes growth and sexual maturation.

There are potential concerns regarding starting life-long ART in all children. Drug choices are more limited in children than in adults, and adequate data on the potential long-term toxicities of prolonged ART in a developing child are not yet available. Some studies have shown that a small proportion of children with perinatally acquired HIV may be long-term non-progressors. These children have no immunologic or clinical progression by age 10 years, despite receiving no ART.[74-76] Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in children is often challenging.[77] Incomplete adherence leads to the selection of drug resistance mutations, but forcibly administrating ARV drugs to children may result in treatment aversion or fatigue, which occurs among many children with perinatally acquired HIV during adolescence.[78]

Despite this, a number of studies have found evidence for the long-term benefits of early ART, including reduced mortality in children aged <10 years,[14] improved growth and pubertal outcomes, improved immune reconstitution, and reduced inflammation in children and adolescents. The Panel believes the benefits of early ART initiation outweigh the potential risks, and recommends initiating ART in all children regardless of clinical, immunologic, or virologic status.

On a case-by-case basis, patients, caregivers, and providers may collaboratively decide to defer therapy due to clinical and/or psychosocial factors. If therapy is deferred, the health care provider should closely monitor a child's virologic, immunologic, and clinical status every 3 to 4 months **(AIII)** (see Clinical and Laboratory Monitoring of Pediatric HIV Infection). Factors to consider when deciding when to initiate therapy in children for whom treatment was deferred include:

- Increasing HIV RNA levels;

- Declining CD4 cell count or percentage values (e.g., approaching CDC Stage 2-3);

- Development of new clinical symptoms; *and*

- The ability of a caregiver and child to adhere to the prescribed regimen.

Table 5. HIV Infection Stage Based on Age-Specific CD4 Cell Count or Percentage

Stage[a]	Age at the Time of the CD4 Test					
	<1 Year		1 Year to <6 Years		≥6 Years	
	Cells/μL	%	Cells/μL	%	Cells/μL	%
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 cell count; the CD4 cell 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.

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.

Key to Acronyms: CD4 = CD4 T lymphocyte

Table 6. HIV-Related Symptoms and Conditions

Mildly Symptomatic
Children with two or more of the conditions listed, but none of the conditions listed in the Moderate Symptoms category: • 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 • Cytomegalovirus 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

Table 6. HIV-Related Symptoms and Conditions, continued

AIDS-Defining Conditions, continued
• Cervical cancer, invasive[b]
• 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[c]
• 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[b]
• Progressive multifocal leukoencephalopathy
• Salmonella septicemia, recurrent
• Toxoplasmosis of brain, onset at age >1 month
• Wasting syndrome attributed to HIV[c]

[a] Only among children aged <6 years.

[b] Only among adults, adolescents, and children aged ≥6 years.

[c] 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).

Key to Acronyms: CDC = Centers for Disease Control and Prevention; 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.

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What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

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

Criteria Used for Recommendations

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

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

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;

- The extent of pediatric experience with a specific drug or regimen;

- Incidence and types of short-term and long-term drug toxicity in people who are taking the regimen, focusing on toxicities that are reported in children;

- 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*

- Potential for drug interactions with other medications.

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

- *Preferred:* Drugs or drug combinations are designated as *Preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies using surrogate markers have demonstrated safety and efficacy. Additional considerations are listed above.

- *Alternative:* Drugs or drug combinations are designated as *Alternative* for initial therapy when clinical trial data in children or adults show efficacy, but the drugs and drug combinations have disadvantages when compared with *Preferred* regimens. These disadvantages include: more limited experience with use of the drugs or regimen in children than in adults; the extent of antiviral efficacy or durability is less well defined in children, or the drug or regimen is less effective or durable than a *Preferred* regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.

Factors to Consider When Selecting an Initial Regimen

An ART regimen for children should generally consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an active drug from one of the following classes: integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Choice of a regimen should be individualized based on several factors, including the characteristics of the proposed regimen; the patient's age, weight, sexual maturity rating (SMR), and other characteristics; and the results of viral resistance testing. Drug recommendations often include both age and weight limitations. Although age can be used as a rough guide, body weight (when available) is the preferred determinant for selecting a specific drug. An exception to this guide is for infants who are less than 14 days of age. 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 Perinatal HIV. The advantages and disadvantages of each regimen are described in detail in the sections that follow and in Table 8. Additional information regarding the advantages and disadvantages of specific drug combinations can be found in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. Specific information about the clinical efficacy, adverse events (AEs), and dosing recommendations for each drug can be found in Appendix A: Pediatric Antiretroviral Drug Information. In addition, because ART will most likely need to be administered throughout the patient's life, clinicians should consider potential barriers to adherence. These barriers may include complex dosing schedules, food requirements, the need to use multiple formulations to achieve an appropriate dose, palatability problems, and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after the patient has been assessed and the clinician has counseled the patient and caregivers about adherence to therapy.

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

Choosing an Initial Antiretroviral Regimen for Children with HIV

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

Clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a

PI-based regimen for initial therapy. Three pediatric studies have compared an NNRTI-based regimen to a PI-based regimen, and results varied based on the age of the population studied and the specific drug used within the class.

- The P1060 study demonstrated the superiority of a lopinavir/ritonavir (LPV/r)-based regimen over a nevirapine-based regimen in infants and children aged 2 months to 35 months, regardless of maternal or infant exposure to peripartum, single-dose nevirapine prophylaxis. In children with prior nevirapine exposure, 21.7% of children receiving the LPV/r-based regimen experienced death, virologic failure, or toxicity by Week 24 compared to 39.6% of children receiving the nevirapine-based regimen. For children with no prior nevirapine exposure, death, virologic failure, and toxicity occurred in 18.4% of children receiving the LPV/r-based regimen and 40.1% of children receiving the nevirapine-based regimen.[1]

- Those in the nevirapine group demonstrated greater, but not statistically significant, improvements in CD4 counts and growth parameters. However, improvements in CD4 cell counts were only maintained up to 1 year after initiation of ART.[2] Similar improved immune and growth parameters were also reported in the NEVEREST study, where these parameters were compared in children who switched to a nevirapine-containing regimen and those who continued on a LPV/r-containing regimen after achieving virologic suppression.[3] Improvements in metabolic parameters have also been seen in children who switched from LPV/r to efavirenz at or after 3 years of age.[4]

- PENPACT-1 (PENTA 9/PACTG 390) compared a PI-based regimen and a NNRTI-based regimen in treatment-naive children aged 30 days to <18 years (the study did not dictate the specific NNRTI or PI). 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 efavirenz and 38% received nevirapine. 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 ART regimen. In both groups, 82% of children had viral loads <400 copies/mL.[5]

- The PROMOTE-pediatrics trial demonstrated comparable virologic efficacy among children who were randomized to receive either an NNRTI-based or a LPV/r-based ART regimen.[6] Children were aged 2 months to <6 years and had no perinatal exposure to nevirapine. Selection of the NNRTI was based on age (children aged <3 years received nevirapine, and those aged >3 years primarily received efavirenz). The proportion of children with HIV RNA levels <400 copies/mL at 48 weeks was 80% in the LPV/r arm versus 76% in the NNRTI arm, a difference of 4% that was not statistically significant (95% confidence interval [CI], -9% to +17%).

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

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

- Children aged <14 days: Nevirapine

- Children aged <14 days and weighing ≥2 kg: Raltegravir

- Children aged ≥14 days to <3 years: LPV/r or raltegravir

- Children aged ≥3 years and
  - Weighing <25 kg: Atazanavir, atazanavir/ritonavir (ATV/r), twice-daily darunavir/ritonavir (DRV/r), or raltegravir
  - Weighing ≥25 kg: Dolutegravir

- **Weighing ≥25 kg:** Elvitegravir/cobicistat (only the fixed-dose combination [FDC] elvitegravir/cobicistat/emtricitabine/TAF is recommended at this time)

Alternative regimens are shown in Table 7 below.

Integrase Strand Transfer Inhibitor-Based Regimens

Four INSTIs—bictegravir, dolutegravir, elvitegravir, and raltegravir—are approved by the FDA for treating antiretroviral (ARV)-naive adults with HIV. These agents have quickly become the recommended regimens in adults because of their virologic efficacy, lack of drug interactions, and favorable toxicity profile. Raltegravir is approved for the treatment of infants and children from birth onwards with weights ≥2 kg. Dolutegravir is approved for use in children weighing ≥30 kg. Elvitegravir has been studied in adolescents in two FDC regimens and in combination with two NRTIs and ritonavir boosting. The use of bictegravir in children and adolescents is currently being investigated; for more information, see What Not to Start. Table 8 lists the advantages and disadvantages of using INSTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

Dolutegravir

The FDA has approved dolutegravir for use in children weighing ≥30 kg. The approval was supported by data from a study of 46 treatment-experienced (but INSTI-naive) adolescents[9,10] and 11 treatment-experienced (but INSTI-naive) children aged ≥6 years.[11] The World Health Organization (WHO) recommends using dolutegravir in children weighing ≥25 kg. This recommendation is based on PK and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY). The Panel agrees with the WHO assessment that dolutegravir can be used in children weighing ≥25 kg (see the dolutegravir section); it has a very favorable safety profile and can be given once daily to treat INSTI-naive patients. Studies of dolutegravir are ongoing in children as young as 4 weeks of age.[12]

In a prospective surveillance study of birth outcomes among pregnant women on ART in Botswana, an increased risk of neural tube defects (NTDs) was observed among infants born to women who were receiving dolutegravir at the time of conception.[13,14] These findings should be considered when deciding on an ART regimen for female adolescents of childbearing potential. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Recommendation:

- Dolutegravir plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for children and adolescents weighing ≥25 kg **(AI*)**. The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.[7,9,15]

- Dolutegravir **is not recommended** for use in adolescents and women who are trying to conceive or who may become pregnant, due to concerns about a possible increased risk of NTDs.

Elvitegravir

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

Recommendation:

- Elvitegravir/cobicistat/emtricitabine/TAF is recommended as a *Preferred* 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.[16-21]

Raltegravir

Raltegravir 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 raltegravir-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 Perinatal HIV.

Recommendation:

- Raltegravir plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants and children from birth to age 3 years who weigh ≥2 kg and for children aged ≥3 years and weighing <25 kg **(AI*)**. It is an *Alternative* INSTI-based regimen for children aged ≥3 years and weighing ≥25 kg **(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.[7,22-29] The Panel acknowledges that data regarding the efficacy of this agent in those aged <2 years are currently very limited.[30]

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

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Efavirenz (for children aged ≥3 months), etravirine (for children aged ≥6 years), nevirapine (for children aged ≥15 days), and rilpivirine (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 for less-frequent drug administration, a lower risk of dyslipidemia and fat maldistribution than some agents in the PI class, and, generally, a lower pill burden than PIs. However, a single viral mutation can confer high-level drug resistance to all NNRTIs except etravirine, 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 nevirapine, 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 lists the advantages and disadvantages of using NNRTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information for each drug.

Efavirenz

Although efavirenz 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 efavirenz in very young patients can be highly variable.

Recommendation:

- Efavirenz 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.[15,22,31-49]

Nevirapine

There are extensive clinical and safety data for the use of nevirapine in children with HIV, and nevirapine has shown ARV efficacy when used as a component in a variety of combination regimens.[1,5,6,50-54] Nevirapine has

also been used extensively as prophylaxis for the prevention of HIV transmission in young infants during the peripartum period and during breastfeeding. The safety and PKs of nevirapine have been studied at the low doses of the drug that are used for prophylaxis. There is currently less information available from studies in very young infants about the safety and PKs of the higher nevirapine doses that are necessary for treatment. Early testing of infants allows HIV infection to be confirmed before 14 days of age. In these cases, the Panel recommends the use of nevirapine as a *Preferred* NNRTI when a clinician plans to initiate treatment prior to age 14 days. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcomes compared to starting after age 14 days. Clinicians should consult an expert in pediatric HIV infection when considering the use of nevirapine in infants aged <14 days. Additional considerations regarding the use of nevirapine in infants aged <14 days can be found in Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV.

Recommendation:

- Nevirapine plus a two-NRTI backbone is recommended as a *Preferred* NNRTI-based regimen in infants aged <14 days and an *Alternative* NNRTI-based regimen for children aged ≥14 days to <3 years **(AI)**. A change from nevirapine to LPV/r should be considered after 14 days of life and a post-gestational age of 42 weeks, as LPV/r has better clinical outcomes than nevirapine in children aged <3 years. The Panel recommends switching from nevirapine to LPV/r in these patients because nevirapine is associated with rare occurrences of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, and rare (but potentially life-threatening) instances of hepatitis. Nevirapine also has a low barrier to resistance, and there is conflicting data about the virologic efficacy of nevirapine compared to *Preferred* regimens.[1,5,6,52-64]

Rilpivirine

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

Recommendation:

- Rilpivirine 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 rilpivirine in adolescents and the larger body of evidence in adults.[38,65-69]

Protease Inhibitor-Based Regimens

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

Ritonavir 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 ritonavir boosting increases the risk of hyperlipidemia[70] and drug interactions.

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

Atazanavir/Ritonavir

Atazanavir 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. Atazanavir is most often boosted with ritonavir. Approval was extended in 2014 for use in infants and children aged ≥3 months and weighing ≥5 kg. Atazanavir administered in combination with cobicistat has been approved by the FDA for use in adults. The use of this combination in children and adolescents is under investigation, but no data are currently available.[71,72]

Recommendation:

- ATV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for children aged ≥3 years and weighing <25 kg, and as an *Alternative* PI-based regimen for children aged ≥3 months to <3 years and children aged ≥3 years and weighing ≥25 kg **(AI*)**. This regimen has been shown to be virologically potent in adult and pediatric studies, and it has 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.[25,34,67,70,73-78]

- The Panel **does not recommend** the use of unboosted ATV.

Darunavir/Ritonavir

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 ARV-experienced patients who do not have DRV resistance-associated mutations. Once-daily dosing of DRV/r was investigated during a substudy of a twice-daily dosing trial in children aged 3 years to <12 years. This PK evaluation lasted only 2 weeks, after which the participants switched back to the twice-daily regimen.[79] FDA dosing recommendations are based on PK models from this study, but this dose has never undergone trials for clinical efficacy in this age group. A more recent study also suggested that once-daily DRV/r dosing is acceptable for children and adolescents. In this study, the plasma concentration-time curve for DRV/r was substantially lower than the mean value observed in adults; however, trough levels were similar. Because of these findings, and due to the lack of more information about the efficacy of once-daily DRV/r dosing in treatment-naive and treatment-experienced children aged <12 years, the Panel recommends a twice-daily dose of DRV/r in children aged >3 years to <12 years.[80]

Recommendation:

- DRV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for children aged ≥3 years and weighing ≥10 kg but <25 kg, and as an *Alternative* PI-based regimen for children aged ≥3 years and weighing ≥25 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 development of drug resistance and excellent toxicity profile in adults and children.[25,80-87]

- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of an *Alternative* PI-based regimen in treatment-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 if the following darunavir resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

Lopinavir/Ritonavir

LPV/r is approved 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,[88] but PK data in children do not support a recommendation for once-daily dosing.[89-91]

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 <3 years **(AI)** and as an *Alternative* PI-based regimen in children aged ≥3 years **(AI*)**. This regimen has been shown to be virologically potent in adult and pediatric studies and has been well tolerated in pediatric studies.[15,36,73,74,81,88-90,92-96]

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

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, eight NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, TDF, and TAF) are approved by the FDA for use in children aged <13 years. Dual-NRTI combinations that have been studied in children include:

- Zidovudine used in combination with abacavir, didanosine, or lamivudine

- Abacavir used in combination with lamivudine, stavudine, or didanosine

- Emtricitabine used in combination with stavudine or didanosine

- TDF used in combination with lamivudine or emtricitabine

- TAF used in combination with emtricitabine[20,44,75,97-101]

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. The advantages and disadvantages of different dual-NRTI backbone options that are recommended for initial therapy are listed in Table 8. See What Not to Start for more information. Also, see Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

In the dual-NRTI regimens listed below, lamivudine and emtricitabine are interchangeable. Both lamivudine and emtricitabine are well tolerated and have few AEs. Emtricitabine is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine used in combination with abacavir or TDF or zidovudine). The main advantage of emtricitabine over lamivudine is that it can be administered once-daily as part of an initial regimen. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs, a modest decrease in susceptibility to abacavir, and improved susceptibility to zidovudine and TDF based on decreased viral fitness.[102,103]

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

Abacavir in Combination with Lamivudine or Emtricitabine

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

Recommendation:

- Abacavir plus lamivudine or emtricitabine is recommended as the *Preferred* dual-NRTI combination for children aged ≥3 months **(AI)**. Studies of adults and children have reported virologic efficacy and favorable toxicity profiles for these combinations.[23,104-111]

- Once-daily dosing of abacavir is recommended when using the pill formulation. Twice-daily dosing of liquid abacavir 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 cell counts.[112-115]

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 elvitegravir, cobicistat, and emtricitabine 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.[21] An FDC tablet that contains emtricitabine/TAF (Descovy) is also available.

Recommendation:

- Emtricitabine/TAF is recommended as a *Preferred* dual-NRTI combination in children and adolescents weighing ≥25 kg who have estimated CrCl ≥30 mL/min when this combination is used with an INSTI or NNRTI; this combination is considered a *Preferred* dual-NRTI combination when used with a PI in children and adolescents weighing ≥35 kg who have estimated CrCl ≥30 mL/min **(AI*)**. This combination is also recommended as a *Preferred* drug combination when used in the single-tablet regimen elvitegravir/cobicistat/emtricitabine/TAF for children and adolescents weighing ≥25 kg **(AI*)**. The Panel makes these recommendations because TAF has a lower risk of renal and bone AEs than TDF.[18,116]

- Emtricitabine/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 ART regimen. Decreases in bone mineral density (BMD) have been observed in adults and children receiving TDF, but the clinical significance of these decreases is unknown.[98-101,117,118] Before starting treatment, clinicians should consider whether the benefits of using TDF outweigh the potential risks of decreased BMD.[119]

Recommendation:

- TDF plus lamivudine or emtricitabine 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.[98-101,105-108,120-125]

Zidovudine in Combination with Abacavir

Zidovudine plus abacavir had lower rates of viral suppression and a greater number of toxicities that lead to regimen modification than did abacavir plus lamivudine in a European pediatric study.[97,104]

Recommendation:

- Zidovudine plus abacavir is recommended as an *Alternative* dual-NRTI combination for children aged ≥3 months **(BII)**.

Zidovudine in Combination with Lamivudine or Emtricitabine

Zidovudine 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 in infants aged ≥4 weeks and prophylaxis in newborns.

Recommendation:

- Zidovudine plus lamivudine or emtricitabine is recommended as a *Preferred* dual-NRTI combination for infants and children from birth to age ≤6 years, and an *Alternative* combination in children aged ≥6 years and adolescents **(AI*)**. The Panel bases these recommendations on the extensive experience and favorable safety profiles for these combinations. There is extensive experience with these dual-NRTI backbones in children, and they have been shown to have favorable safety profiles. However, twice-daily dosing is required for zidovudine in children aged ≥6 years. Other NRTIs that only require once-daily

dosing in in children aged ≥6 years are available.[109,126-128]

- Zidovudine plus abacavir is recommended as an *Alternative* dual-NRTI combination for use in children aged ≥3 months **(BII)**. In children aged ≥6 years and adolescents who are not sexually mature (i.e., those with SMRs 1–3), the Panel recommends zidovudine plus lamivudine or emtricitabine as an *Alternative* dual-NRTI combination **(BII)**.

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

Patient Age and Weight Class

	Birth to <14 Days of Age[a,b,c]	Children Aged ≥14 Days to <3 Years	Children Aged ≥3 Years and Weighing <25 kg	Children Aged ≥3 Years and Weighing ≥25 kg
INSTI-Based Regimens	Two NRTIs **plus** RAL[c]			
				Two NRTIs **plus** DTG[d]
				Two NRTIs **plus** EVG/c[e]
NNRTI-Based Regimens	Two NRTIs **plus** NVP[a,f]			
PI-Based Regimens		Two NRTIs **plus** LPV/r[b]		
			Two NRTIs **plus** ATV/r	
			Two NRTIs **plus** DRV/r[g]	

[a] If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are the *Preferred* agents because they are the only options with dosing information available for this age group. However, available clinical trial data does not suggest that initiating treatment within the first 14 days of life is more beneficial than starting treatment after 14 days of age. 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 Perinatal HIV. Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) of 42 weeks; LPV/r has produced better clinical outcomes in studies of children aged <3 years than NVP. Data are limited on the clinical outcomes of using RAL in infants and children aged <2 years.

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

[c] RAL can be used in infants weighing ≥2 kg. RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered to infants and children from birth to age 2 years.

[d] DTG is recommended only for use in children and adolescents weighing ≥25 kg. For children weighing <25 kg, the use of RAL can be considered when an INSTI-based regimen is desired.

[e] EVG is currently recommended only as a component of FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as a *Preferred* regimen for children and adolescents weighing ≥35 kg, and as an *Alternative* regimen for children and adolescents weighing ≥25 kg.

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

[g] Once-daily DRV should not be used in children aged <12 years or weighing <40 kg. Once-daily DRV should also not be used if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is recommended as an *Alternative* drug combination for children aged ≥6 years to <12 years, because there are other drugs that can be administered once daily. This combination is considered a *Preferred* option for adolescents aged ≥12 years with SMR 1–3 when once-daily administration is possible.

Key to Acronyms: ATV/r = atazanavir/ritonavir; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; SMR = sexual maturity rating; TAF = tenofovir alafenamide

Table 7. Antiretroviral Regimens Recommended for <u>Initial</u> Therapy for HIV Infection in Children

An ART regimen for treatment-naive children is generally made up of a two-NRTI backbone and either one NNRTI <u>or</u> one INSTI <u>or</u> one PI boosted with RTV or COBI. *Preferred* regimens are designated based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens have also demonstrated efficacy, but clinical experience with these regimens is limited or these regimens are more difficult to administer than *Preferred* regimens. Regimens should be tailored to the individual patient by weighing the advantages and disadvantages of each combination. Many agents have multiple formulations and age and weight recommendations. Please consult Appendix A: Pediatric Antiretroviral Drug Information for additional information and recommended dosages and formulations (see Table 8 below).

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

Preferred Regimens			
Age	**Regimens**		**FDC Available** (see Fixed-Dose Combinations)
Infants, Birth to Age <14 Days[a,b]	Two NRTIs **plus** NVP		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** LPV/r		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	Weight <25 kg	Two NRTIs **plus** ATV/r	No
		Two NRTIs **plus** twice-daily DRV/r[d]	No
		Two NRTIs **plus** RAL[c]	No
	Weight ≥25 kg	Two NRTIs **plus** DTG[f]	Yes
		Two NRTIs **plus** EVG/COBI[e]	Yes
Adolescents Aged ≥12 Years with SMR 4 or 5	Refer to the Adult and Adolescent Antiretroviral Guidelines		Yes
Alternative Regimens			
Age	**Regimens**		**FDC Available**
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** NVP[g]		No
Children Aged ≥3 Months to <3 Years	Two NRTIs **plus** ATV/r		No
Children Aged ≥3 Years and Weighing ≥25 kg	Two NRTIs **plus** ATV/r		No
	Two NRTIs **plus** DRV/r[d]		No
	Two NRTIs **plus** RAL[c]		No
Children Aged ≥3 Years	Two NRTIs **plus** EFV[h]		No[i]
	Two NRTIs **plus** LPV/r		No
Adolescents Aged ≥12 Years with SMR 1–3	Weight ≥35 kg	Two NRTIs **plus** RPV[j]	Yes
Adolescents Aged ≥12 Years with SMR 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**
Children, Birth to Age <3 Months	ZDV **plus** (3TC **or** FTC)[k]		No
Children Aged ≥3 Months to <6 Years	ABC **plus** (3TC **or** FTC)[l]		Yes
	ZDV **plus** (3TC **or** FTC)[k]		Yes
Children and Adolescents Aged ≥6 Years with SMR 1–3	ABC **plus** (3TC **or** FTC)[l]		Yes
	Weighing ≥25 kg and receiving a regimen that contains an INSTI or an NNRTI	FTC/TAF[m]	Yes

Table 7. Antiretroviral Regimens Recommended for <u>Initial</u> Therapy for HIV Infection in Children, continued

Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs		
Age	**Dual-NRTI Backbone Options**	**FDC Available**
Adolescents Aged ≥12 Years with SMR 4 or 5	Refer to the <u>Adult and Adolescent Antiretroviral Guidelines</u>	Yes
Alternative Dual-NRTI Backbone Options for Use in Combination with Other Drugs		
Age	**Dual-NRTI Backbone Options**	**FDC Available**
Children Aged ≥3 Months	ZDV **plus** ABC	No
Children Aged ≥2 Years to 12 Years	TDF **plus** (3TC **or** FTC)[n]	Yes
Children and Adolescents Aged ≥6 Years and SMR 1–3	ZDV **plus** (3TC **or** FTC)[k]	Yes

[a] If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are *Preferred* agents because they are the only options with dosing information available for this age group. While many pediatric experts favor initiating ART as soon as possible after birth in order to limit the establishment of viral reservoirs, available clinical trial data does 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 <u>Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV</u>. Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth); LPV/r has produced better clinical outcomes in studies of children aged <3 years than NVP. Data are limited on the clinical outcomes of using RAL in infants and children aged <2 years.

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

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children from birth to age 2 years. No dosing information is available for preterm infants or those with a weight of < 2 kg at birth.

[d] 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).

[e] EVG is currently recommended only as a component of FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as a *Preferred* regimen for children and adolescents weighing ≥35 kg, and as an *Alternative* regimen for children and adolescents weighing ≥25 kg.

[f] DTG is recommended as a *Preferred* agent for children and adolescents weighing ≥25 kg. An FDC tablet containing ABC/DTG/3TC (Triumeq) is available.

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

[h] EFV is approved by the FDA for use in children aged ≥3 months and weighing ≥3.5 kg, but it **is not recommended** by the Panel for initial therapy in children aged ≥3 months to 3 years. An FDC tablet containing EFV/FTC/TDF (Atripla) and EFV 600 mg/3TC/TDF (Symfi) is available. See efavirenz section for information about use of the FDC EFV 400 mg/3TC TDF (Symfi Lo).

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

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

[k] An FDC containing 3TC/ZDV (Combivir and generic) is available.

[l] An FDC containing ABC/3TC (Epzicom and generic) is available.

[m] FTC/TAF is recommended as a *Preferred* combination for children and adolescents weighing ≥25 kg; an FDC containing FTC/TAF is available. FTC/TAF is approved by the FDA for children weighing ≥25 kg when used in the single-tablet regimen EVG/COBI/FTC/TAF or as TAF/FTC in combination with an NNRTI or INSTI. FTC/TAF plus a boosted PI is only recommended for use in children and adolescents weighing ≥35 kg.

[n] An FDC containing FTC/TDF (Truvada) is available.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for <u>Initial Therapy in Children</u> (page 1 of 4)

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order	All INSTIs	INSTI Class Advantages: • Few drug-drug interactions • Well-tolerated	INSTI Class Disadvantages: • Limited data on pediatric dosing or safety
	DTG	Once-daily administration Can give with food Available in FDC tablets (see Fixed-Dose Combinations) Single-agent DTG pills are available in several dosages and are small in size.	Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing of DTG CNS side effects, particularly sleep disturbances and possible increased risk of neural tube defects in infants born to women who were receiving dolutegravir at the time of conception
	EVG	Once-daily administration Available in FDC tablets (see Fixed-Dose Combinations)	Among INSTIs, EVG has the lowest barrier to the development of resistance. If EVG is administered with COBI, there is potential 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 Once-daily administration (with RAL HD) can be used for treatment-naive or virologically suppressed children weighing ≥50 kg.	Potential for rare systemic allergic reaction or hepatitis Granule formulation requires a multistep preparation before administration; caregiver must be taught how to properly prepare this formulation.
NNRTIs In Alphabetical Order	All NNRTIs	NNRTI Class Advantages: • Long half-life • Lower risk of dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking the solid formulation; easier to use and adhere to than PI-based regimens	NNRTI Class Disadvantages: • A single mutation can confer resistance, with cross-resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity. All NNRTIs pose this risk, but the risk is greatest with NVP. • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	Once-daily administration Available in FDC tablets (see Fixed-Dose Combinations) 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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs In Alphabetical Order, continued	NVP	Liquid formulation is available. Dosing information for young infants is available. Can give with food Extended-release formulation is available that allows for once-daily dosing in older children.	Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen Higher incidence of rash/HSR than other NNRTIs Higher rates of serious hepatic toxicity than EFV Decreased virologic response compared with EFV Twice-daily dosing necessary in children with BSA <0.58 m^2 Low barrier for resistance
	RPV	Once-daily dosing Available in FDC tablets (see Fixed-Dose Combinations)	Should not use in patients with HIV 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 for resistance
PIs In Alphabetical Order	All PIs	PI Class Advantages: • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well-documented. • Resistance to PIs requires multiple mutations. • When combined with a dual-NRTI backbone, a regimen containing 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 PR interval of ECG). RTV is associated with a large number of drug interactions.
	Boosted DRV	Can be used once daily in children aged ≥12 years Liquid formulation is available. DRV requires a boosting agent. Available in FDC tablets (see Fixed-Dose Combinations)	Pediatric pill burden high with current tablet dose formulations Should be administered with food Must be boosted to achieve adequate plasma concentrations Contains sulfa moiety. The potential for cross-sensitivity between DRV and other drugs in sulfonamide class is unknown. RTV is associated with a large number of drug interactions. Can only be used once daily in the absence of certain PI-associated resistance mutations

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for <u>Initial</u> Therapy in Children[a] (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	LPV/r	LPV is only available coformulated with RTV in liquid and tablet formulations. Tablets can be given without regard to food, but they may be better tolerated when taken with meal or snack.	Poor palatability of liquid formulation (bitter taste), although the palatability of the FDC is better than RTV alone 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 (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) of 42 weeks and a postnatal age ≥14 days Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	Palatable liquid formulations Can give with food Available in FDC tablets (see Fixed-Dose Combinations)	Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.
	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 Fixed-Dose Combinations)	Limited data on the safety and efficacy of this combination in children Increased lipid levels
	TDF **plus** (3TC **or** FTC) for adolescents with SMR 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 Fixed-Dose Combinations)	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 with ZDV Lipoatrophy with ZDV
	ZDV **plus** ABC	Palatable liquid formulations Can give with food	Risk of ABC HSRs; perform HLA-B*5701 screening before initiation of ABC treatment. Bone marrow suppression and lipoatrophy with ZDV

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for <u>Initial</u> Therapy in Children[a] (page 4 of 4)

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

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Many antiretroviral (ARV) agents and combinations are available; some are not recommended for use as part of an initial regimen in ARV-naive children, although they may be used in ARV-experienced children. This section describes ARV drugs and drug combinations that are not recommended for use in ARV-naive children, or that lack sufficient data to recommend their use in ARV-naive children. Several ARV drugs that are no longer available or that have not been recommended for use in in children for several years, including the nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and didanosine and the protease inhibitors (PIs) indinavir, nelfinavir, saquinavir, tipranavir, fosamprenavir, and enfuvirtide, have been removed from this chapter. Information about these agents is available in Archived Drugs.

Not Recommended

These include 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 there are better options within a drug class. These drugs and drug combinations are listed in Table 9.

Insufficient Data to Recommend

Drugs and drug combinations that are approved for use in adults but that have insufficient, limited, and/or no pharmacokinetic (PK) 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 are also listed in Table 9.

Antiretroviral Drugs and Combinations Not Recommended for Initial Therapy

Several ARV drugs, or certain dosing schedules for some ARV drugs, may be appropriate for use in some children but not others, depending on the child's age and weight.

Atazanavir without Ritonavir Boosting

Although unboosted atazanavir is approved by the Food and Drug Administration (FDA) for use in treatment-naive adolescents aged ≥13 years and weighing ≥40 kg who are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (as measured by mg/m^2 of body surface area) are required in adolescents than in adults to achieve adequate drug concentrations.[1] The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** using atazanavir without ritonavir boosting because of these findings.

Regimens Containing 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 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 Containing Three Drug Classes

Data are insufficient to recommend initial regimens that contain agents from three drug classes (e.g., an NRTI plus an NNRTI plus a PI or an integrase strand transfer inhibitor [INSTI] 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 as treatment in neonates.

Regimens Containing Three Nucleoside Reverse Transcriptase Inhibitors and a Non-Nucleoside Reverse Transcriptase Inhibitor

Data are currently 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 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 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 dual-NRTI plus NNRTI regimen or a three-NRTI regimen. Although early improvements in CD4 T lymphocyte (CD4) cell counts and virologic control were observed among patients in the four-drug arm, these benefits were not sustained after patients switched to the three-NRTI regimen.[13] Furthermore, after a median of 3.7 years on therapy, children in the four-drug arm who changed to an all-NRTI regimen had significantly poorer virologic control.[14] Because three-drug regimens have been shown to be effective and well tolerated, and because efficacy data is lacking for the four-drug regimen, the Panel does not currently 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 appear promising for use in adults 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 due to insufficient data. As new data become available, these agents may become recommended agents or regimens. These agents and regimens are summarized below and are also listed in Table 9.

Bictegravir-Based Regimens

Bictegravir is an INSTI that is currently available only as part of a fixed-dose combination (FDC) tablet that contains bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg and is marketed as Biktarvy. Although Biktarvy is now a recommended regimen for initial therapy in adults, there is minimal experience with this drug in children and adolescents. Biktarvy was administered to adolescents aged 12 years to <18 years and weighing ≥35 kg who had maintained viral loads <50 copies/mL for ≥6 months. The drug was well tolerated, all 24 participants in the study had viral loads <50 copies/mL at Week 24, and drug exposure among adolescent patients was similar to the exposure observed in adults. Bictegravir-containing regimens hold promise for use as initial therapy in children and adolescents.[15,16] However, at this time there is insufficient evidence to recommend the use of a bictegravir-based regimen as an initial regimen in children and adolescents.

Doravirine-Based Regimens

Doravirine is an NNRTI that is available as both a single-drug tablet and an FDC that contains doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg and is marketed as Delstrigo. Efficacy studies in adults have demonstrated that doravirine/lamivudine/TDF is noninferior to efavirenz-based regimens and darunavir-based regimens. Doravirine compared favorably to the other drugs in these trials in terms of adverse events. Currently, doravirine is not approved for use in children or adolescents aged <18

years, but there are ongoing studies of doravirine in children and adolescents. At this time, the Panel does not recommend the use of doravirine in children or adolescents.

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

Data are limited on the PKs of once-daily darunavir/ritonavir (DRV/r) in young children. While modeling studies identified a once-daily dosing schedule for this combination that is now approved by the FDA, the Panel is concerned about the lack of efficacy data for individuals aged ≥3 years to <12 years treated with once-daily DRV/r. Therefore, once-daily dosing **is not recommended** 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 the DRV/r dosing to once-daily if no darunavir-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

Efavirenz is approved by the FDA for use in children aged >3 months and weighing ≥3.5 kg. An efavirenz-based regimen has been shown to have variable PKs in studies of the very young; because of this, the Panel does not recommend using efavirenz in children aged <3 years at this time (see the efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information). When use of efavirenz is being considered for children aged <3 years, cytochrome P450 (CYP) 2B6 genotyping should be performed, if available, in order to predict a patient's metabolic rate for efavirenz. Therapeutic drug monitoring can also be considered.

Etravirine-Based Regimens

Etravirine is an NNRTI that has been studied in treatment-experienced children aged ≥1 years and is now approved by the FDA for use in children aged ≥2 years and weighing ≥10 kg.[17-19] It is associated with multiple interactions with other ARV drugs, including tipranavir/ritonavir, atazanavir/ritonavir, and unboosted PIs, and must be administered twice daily. It is unlikely that etravirine will be studied in treatment-naive children.

Maraviroc-Based Regimens

Maraviroc is an entry inhibitor that is approved by the FDA for use in children aged ≥2 years and weighing ≥10 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 maraviroc to treatment-experienced children aged 2 years to 18 years who were divided into four age cohorts.[20] Initial dose was based on body surface area and scaled from recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP3A4 inhibitor or inducer.[21] Maraviroc has multiple drug interactions and must be administered twice daily. In addition, tropism assays must be performed prior to use to ensure the presence of only CCR5-tropic virus.

Antiretroviral Drug Regimens That Are Never Recommended

Several ARV drugs and drug regimens should never be used in children or adults. These are summarized in Table 10. Clinicians should also be aware of the components of FDC tablets so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

Table 9. Antiretroviral Therapy Regimens or Components <u>Not</u> Recommended for Initial Treatment of HIV Infection in Children

Regimen or ARV Component	Rationale
Unboosted **ATV**-containing regimens in children	Reduced exposure
BIC-based regimens	Insufficient data to recommend
Once-daily **DRV**-based regimens in children aged ≥3 years to 12 years	Insufficient data to recommend
Unboosted **DRV**	Use without **RTV** has not been studied
Dual (full-dose) PI regimens	Insufficient data to recommend Potential for added toxicities
Dual-NRTI combination of **ABC plus TDF**	Insufficient data to recommend
EFV-based regimens for children aged <3 years	Appropriate dose not determined
ETR-based regimens	Insufficient data to recommend
LPV/r dosed once daily	Reduced drug exposure
MVC-based regimens	Insufficient data to recommend
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Insufficient data to recommend
Full-dose **RTV** or use of **RTV** as the sole PI	GI intolerance Metabolic toxicity
Regimens containing three NRTIs and one NNRTI	Added cost and complexity outweighs any benefit
TDF-containing regimens in children aged <2 years	Potential bone toxicity Appropriate dose has yet to be determined

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; DRV = darunavir; EFV = efavirenz; ETR = etravirine; GI = gastrointestinal; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

Table 10. Antiretroviral Therapy Regimens or Components <u>Never</u> Recommended for Treatment of HIV Infection in Children

ART Regimens <u>Never</u> Recommended for Children		
Regimen	**Rationale**	**Exceptions**
One ARV Drug Alone (Monotherapy)	Rapid development of resistance Inferior antiviral activity compared to combinations that include ≥3 ARV drugs Monotherapy "holding" regimens are associated with more rapid CD4 cell count declines than nonsuppressive ART.	Infants with perinatal HIV exposure and negative virologic tests who are receiving 4 weeks to 6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
Two NRTIs Alone	Rapid development of resistance Inferior antiviral activity compared to combinations that include ≥3 ARV drugs	Not recommended for initial therapy Some clinicians may opt to continue this treatment in patients who are currently on two NRTIs alone and who achieve virologic goals.
TDF plus ABC plus (3TC <u>or</u> 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
TDF plus ddI plus (3TC <u>or</u> 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
ARV Components <u>Never</u> Recommended as Part of an ART Regimen for Children		
Regimen	**Rationale**	**Exceptions**
Dual-NNRTI Combinations	Enhanced toxicity	No exceptions
Dual-NRTI Combination 3TC plus FTC	Similar resistance profile and no additive benefit	No exceptions
Dual-NRTI Combination d4T plus ZDV	Antagonistic effect on HIV	No exceptions
NVP as Initial Therapy in Adolescent Girls with CD4 Cell Counts >250 cells/ mm³ or Adolescent Boys with CD4 Cell 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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; DRV = darunavir; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV <mark>(Last Updated December 14, 2018; last reviewed December 14, 2018)</mark>

Panel's Recommendations
• All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
• Newborn ARV regimens—at gestational-age-appropriate doses—should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.
• The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of perinatal transmission of HIV **(AIII)**. The uses of ARV regimens in newborns include:
• **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.
• **Empiric HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of perinatal acquisition of HIV. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV but 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 dosages (antiretroviral therapy [ART]) to newborns with documented HIV infection (see Diagnosis of HIV Infection).
• For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week zidovudine ARV prophylaxis regimen can be used **(BII)**.
• Newborns at higher risk of perinatal acquisition of HIV should receive a multi-drug ARV prophylaxis regimen or empiric HIV therapy based on clinician assessment of risk (see Tables 11 and 12 for recommended regimens). <mark>Newborns at higher risk of HIV acquisition</mark> include those born to women with HIV who:
• Have not received antepartum or intrapartum ARV drugs **(AI)**, *or*
• Have received only intrapartum ARV drugs **(AI)**, *or*
• Have received antepartum ARV drugs but without viral suppression near delivery **(AII)**, *or*
• Have primary or acute HIV infection during pregnancy **(AII)**, *or*
• Have primary or acute HIV infection during breastfeeding **(AII)**.
• Newborns of women with unknown HIV status who test HIV positive on expedited testing performed during labor or shortly after birth should initiate an ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk) **(AII)**. If supplemental testing is negative, the ARV regimen can be discontinued **(AII)**.
• For newborns with HIV infection, ART should be initiated **(AI)**.
• The use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data **(BIII)**.
• 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 in the neonatal period to reduce perinatal transmission of HIV, with selection of the appropriate ARV regimen guided by the level of transmission risk. The most important factors that influence the risk of HIV transmission to a newborn exposed to HIV are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. The risk of transmission is increased in the absence of maternal ART or if maternal antepartum/intrapartum treatment was started after early pregnancy or was ineffective in producing

virologic suppression; higher maternal viral load, especially in later pregnancy, correlates with higher risk of transmission. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status. HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis since 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 empiric treatment of HIV. In this guideline, 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, as well as combinations of two or three ARV drugs.

- **Empiric HIV Therapy:** The administration of a three-drug ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later documented to have acquired HIV, but 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 treatment regimen to newborns with documented HIV (see Diagnosis of HIV Infection). HIV therapy is lifelong.

The terms ARV prophylaxis and empiric HIV therapy describe the clinician's intent in prescribing ARV drugs and may be overlapping. For example, an empiric HIV therapy regimen also provides ARV prophylaxis for a newborn. However, two-drug (and some three-drug) ARV prophylaxis regimens, notably those that use prophylactic rather than therapeutic dosages of nevirapine, are not considered empiric HIV therapy.

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

Table 11 provides an overview of neonatal ARV management recommendations according to risk of perinatal transmission of HIV to the newborn and Table 12 summarizes the dosing recommendations for ARV dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks gestational age), can be found in Pediatric Antiretroviral Drug Information. In addition, the National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Table 11. Newborn 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 (888-448-8765).

Category	Description	Neonatal ARV Management
Low Risk of Perinatal HIV Transmission	• Mothers who received ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence	ZDV for 4 weeks
Higher Risk of Perinatal HIV Transmission[a,b]	• Mothers who received neither antepartum nor intrapartum ARV drugs • Mothers who received only intrapartum ARV drugs • Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal • Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother **should discontinue** breastfeeding).[c]	2-drug ARV prophylaxis (NICHD-HPTN 040/PACTG 1043 regimen) with 6 weeks ZDV and 3 doses of NVP (prophylactic dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) *or* Empiric HIV therapy using either ZDV, 3TC, and NVP (treatment dosage) *or* ZDV, 3TC, and RAL administered from birth to age 6 weeks.[d]
Presumed Newborn HIV Exposure	• Mothers with unknown HIV status who test HIV positive at delivery or postpartum or whose newborns have a positive HIV antibody test	ARV management as above (for higher risk of perinatal HIV transmission) Infant ARVs 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	3-drug ARV regimen using treatment dosages

[a] See text for evidence supporting a 2-drug ARV prophylaxis regimen and empiric HIV therapy.

[b] See the Intrapartum care section for guidance on indications for scheduled cesarean delivery and intrapartum IV 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 empiric 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, mother should stop breastfeeding.

[d] The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when a birth NAT returns negative, while others would continue empiric HIV therapy for infants at highest risk of HIV acquisition for 6 weeks. In all cases, ZDV should be continued for 6 weeks. It is recommended that providers consult with an expert in pediatric HIV infection to determine therapy duration based on case-specific risk factors and interim HIV NAT results.

[e] Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given low likelihood of a false-positive HIV NAT.

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

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; the Panel = Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; ZDV = zidovudine

Table 12. Antiretroviral Dosing Recommendations for Newborns (page 1 of 2)

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
• ZDV	• ZDV administered for 4 weeks
Newborns at Higher Risk of Perinatal HIV Transmission	
Recommended Regimen	**Recommended Duration**
• 2-drug ARV prophylaxis with ZDV and 3 doses of NVP (NICHD-HPTN 040/PACTG 1043 regimen), *or*	• ZDV administered for 6 weeks; 3 doses of NVP during the first week of life
• Empiric HIV therapy with ZDV/3TC/NVP, *or*	• ZDV administered for 6 weeks; 3TC and NVP administered for 2–6 weeks, up to 6 weeks of age[a]
• Empiric HIV therapy with ZDV/3TC/RAL	• ZDV administered for 6 weeks; 3TC and RAL administered for 2–6 weeks, up to 6 weeks of age[a]
Newborns with HIV Infection	
Recommended Regimen	**Recommended Duration**
• HIV therapy with ZDV/3TC/NVP, *or*	• Lifelong therapy
• HIV therapy with ZDV/3TC/RAL	• Lifelong therapy

Indication			
Drug	**Low Risk Prophylaxis**	**Higher Risk Prophylaxis: 2-Drug**	**Higher Risk Prophylaxis: Empiric <u>and</u> HIV Therapy**
ZDV **Note:** For newborns 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:** • ZDV 4 mg/kg/dose orally twice daily <u>Simplified Weight-Band Dosing for Newborns ≥35 Weeks Gestation at Birth:</u> | **Weight Band (kg)**	**Volume (mL) 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 |		<u>≥35 Weeks Gestation at Birth</u> *Birth–4 Weeks:* • ZDV 4 mg/kg/dose orally twice daily *Age >4 Weeks:* • ZDV 12 mg/kg/dose orally twice daily <u>Simplified Weight-Band Dosing for Newborns Aged ≥35 Weeks Gestation from Birth to 4 Weeks:</u> | **Weight Band (kg)** | **Volume (mL) 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 |
	<u>≥30 to <35 Weeks Gestation at Birth</u> *Birth to Age 2 Weeks:* • ZDV 2 mg/kg/dose orally twice daily *Age 2 Weeks to 4–6 Weeks:* • ZDV 3 mg/kg/dose orally twice daily		<u>≥30 to <35 Weeks Gestation at Birth</u> *Birth to Age 2 Weeks:* • ZDV 2 mg/kg/dose orally twice daily *Age 2 Weeks to 6–8 Weeks:* • ZDV 3 mg/kg/dose orally twice daily *Age >6–8 Weeks:* • ZDV 12 mg/kg/dose orally twice daily
	<u><30 Weeks Gestation at Birth</u> *Birth to Age 4–6 Weeks:* • ZDV 2 mg/kg/dose orally twice daily		<u><30 Weeks Gestation at Birth</u> *Birth to Age 4 Weeks:* • ZDV 2 mg/kg/dose orally twice daily *Age 4 to 8–10 Weeks:* • ZDV 3 mg/kg/dose orally twice daily *Aged >8–10 Weeks:* • ZDV 12 mg/kg/dose orally twice daily
3TC	N/A	N/A	<u>≥32 Weeks Gestation at Birth</u> *Birth to Age 4 Weeks:* • 3TC 2 mg/kg/dose orally twice daily *Age >4 Weeks:* • 3TC 4 mg/kg/dose orally twice daily

Table 12. Antiretroviral Dosing Recommendations for Newborns (page 2 of 2)

	Indication		
Drug	**Low Risk Prophylaxis**	**Higher Risk Prophylaxis: 2-Drug**	**Higher Risk Prophylaxis: Empiric and HIV Therapy**

NVP	N/A	≥32 Weeks Gestation at Birth:
		• NVP in 3 doses given
		  1. Within 48 hours of birth,
		  2. 48 hours after the 1st dose, *and*
		  3. 96 hours after the 2nd dose
		
		Birth Weight 1.5 to 2 kg:
		• NVP 8 mg per dose orally. **Note:** No calculation is required for this dose; **this is the actual dose, not a mg/kg dose**.
		
		Birth Weight >2 kg:
		• NVP 12 mg per dose orally. **Note:** No calculation is required for this dose; **this is the actual dose, not a mg/kg dose**.
			≥37 Weeks Gestation at Birth
			Birth to Age 4 Weeks:
			• NVP 6 mg/kg/dose orally twice daily[b]
			Age >4 Weeks:
			• NVP 200 mg/m^2 of BSA/dose orally twice daily
			
			34 to <37 Weeks Gestation at Birth
			Birth to Age 1 Week:
			• NVP 4 mg/kg/dose orally twice daily
			Age 1 to 4 Weeks:
			• NVP 6 mg/kg/dose orally twice daily
			Age >4 Weeks:
			• NVP 200 mg/m^2 of BSA/dose orally twice daily
			
			Note: NVP dose adjustment at 4 weeks of age is optional for empiric HIV therapy.

RAL **Note**: If the mother has taken RAL 2–24 hours prior to delivery, the neonate's first dose of RAL should be delayed until 24–48 hours after birth; additional ARVs should be started as soon as possible.	N/A	N/A	≥37 Weeks Gestation at Birth and Weighing ≥2 kg[c] *Birth to Age 6 Weeks:* See sub-table below.

Body Weight (kg)	Volume (Dose) of Suspension, RAL 10 mg/mL, to be Administered
Birth to 1 Week: Once Daily Dosing	**Approximately 1.5 mg/kg/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/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/dose**
3 to <4 kg	2.5 mL (25 mg) twice daily
4 to <6 kg	3 mL (30 mg) twice daily

[a] The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue NVP, RAL, and/or 3TC when birth NAT returns negative, while others would continue empiric HIV therapy for infants at the highest risk of HIV acquisition for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, ZDV should be continued for 6 weeks. Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.

[b] Investigational NVP treatment dose recommended by the Panel; FDA has not approved a dose of NVP for infants <1 month of age.

[c] RAL dosing is increased at 1 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 or low birthweight infants.

Key to Acronyms: 3TC = lamivudine; ARV =antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; N/A = no recommendation; NAT = nucleic acid test; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; RAL = raltegravir; UGT1A1 = uridine diphosphate glucotransferase; ZDV = zidovudine

Recommendations for Antiretrovirals in Specific Clinical Situations

In the following sections and Table 11, the Panel on Treatment of Pregnant Women with HIV Infection 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/intrapartum ARV drugs with effective viral suppression
- Are at higher risk of transmitting HIV to their newborns, including mothers who:
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs, *or*
  - Received antepartum and intrapartum ARV drugs but who had detectable viral load near delivery, particularly if delivery was vaginal
- Have acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

Newborns Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression

The risk of HIV acquisition in newborns born to women who received ART regimens during pregnancy and labor and had undetectable viral loads at delivery is <1%. In the PACTG 076 study, zidovudine alone was shown to effectively reduce perinatal HIV transmission and is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week newborn zidovudine regimen was studied in PACTG 076. However, in the United Kingdom and many other European countries, where a 4-week neonatal zidovudine prophylaxis regimen has been recommended for newborns born to mothers who have received ART regimens during pregnancy and have viral suppression, there has been no apparent increase in the overall HIV perinatal transmission rate.[7,8] Compared with the 6-week zidovudine regimen, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.[9]

Therefore, the Panel now recommends a 4-week neonatal zidovudine prophylaxis regimen for newborns if the mother has received ART during pregnancy with viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) at or after 36 weeks gestation, and there are no concerns related to maternal adherence. Dosing recommendations for zidovudine are available for premature newborns and an intravenous preparation is available. Table 12 shows recommended neonatal zidovudine dosing based on gestational age and birthweight.

Newborns Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Who Have Received Intrapartum Antiretroviral Drugs Only, Who Have Received Antiretroviral Drugs and Do Not Have Viral Suppression Near Delivery, or Who Have Acquired HIV During Pregnancy or Breastfeeding

All newborns born to mothers with detectable viral load at the time of delivery, who received only intrapartum ARV drugs, or who have received no ARV drugs during pregnancy or delivery, are at higher risk of HIV acquisition and **should receive a multi-drug ARV prophylaxis regimen or empiric HIV therapy**.[5,10-14] The experience with these regimens is described below. Currently, the optimal duration of an empiric HIV therapy regimen in newborns at higher risk of perinatal HIV transmission is unknown. When birth HIV nucleic acid test (NAT) returns negative, some Panel members would opt to discontinue nevirapine, raltegravir, and/or lamivudine, while others would continue empiric HIV therapy for 6 weeks. In all cases in which the newborn is at higher risk of HIV acquisition, zidovudine should be continued for 6

weeks. Consultation with an expert in pediatric HIV is recommended to select a duration of therapy based on case-specific risk factors and interim HIV NAT results.

For those women who received ARV drugs during pregnancy but have a detectable viral load near delivery (on or after 36 weeks gestation), the level of maternal viremia that would trigger the use of a multi-drug ARV prophylaxis regimen or empiric 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 viral load measurements <50 copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5% when viral load measurements were 50 to 399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.[15,16] However, there has been no study to compare the relative efficacy of a multi-drug ARV prophylaxis regimen or empiric HIV therapy to standard newborn prophylaxis at these different thresholds of maternal viremia. While some Panel members would recommend a multi-drug ARV prophylaxis regimen or empiric HIV therapy with any level of detectable viremia, others reserve multi-drug ARV prophylaxis regimens and empiric HIV therapy until higher levels of maternal viral load are documented. The decision whether to initiate a multi-drug ARV prophylaxis regimen or empiric HIV therapy should be made following discussion with the parents weighing the risks and benefits of the proposed regimen.

Primary or acute HIV infection during pregnancy is associated with an increased risk of perinatal transmission of HIV. A multi-drug ARV prophylaxis regimen or empiric HIV therapy should be administered to the infant until maternal HIV can be confirmed or ruled out. (see Acute HIV Infection).

In summary, in these scenarios where the infant is at higher risk of HIV transmission, the Panel recommends either a multi-drug ARV prophylaxis regimen, specifically the NICHD-HPTN 040/PACTG 1043 regimen, or empiric HIV therapy. The data supporting the use these regimens are summarized below. Choosing between these regimens will depend on clinician assessment of the likelihood of HIV transmission.

Multi-Drug Antiretroviral Prophylaxis

There is a paucity of data from randomized clinical trials to guide the optimal selection of a newborn multi-ARV prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of multi-ARV prophylaxis in newborns at higher risk of HIV acquisition. 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 1 of 3 newborn prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. Forty-one percent of the mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone; $P = 0.046$ for each experimental arm vs. zidovudine alone).[5] The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in 3 of 53 (5.7%) participants with *in utero* infection who were treated with zidovudine alone, and in 6 of 33 (18.2%) participants treated with zidovudine plus nevirapine ($P > 0.05$). In addition, the third drug in the three-arm regimen was nelfinavir, which has highly variable pharmacokinetics (PKs) in this age group and did not reach the nelfinavir target plasma concentration in 46% of study participants.[17] 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 zidovudine-alone regimen (27.5% vs. 15%, $P < 0.0001$).

Data from Europe and the United States indicate increasing use of multi-drug ARV prophylaxis regimens in newborns exposed to HIV. In the United Kingdom and Ireland, use of the regimens increased from 9% of newborns exposed to HIV between 2001 to 2004 to 13% between 2005 to 2008 and, in a poll of 134 U.S.-based providers, 62% reported using multi-ARV prophylaxis regimens in high-risk newborns.[18-20] However, interpretation of these observational studies is complicated by the definition of ARV prophylaxis, use of prophylaxis versus treatment dosing of nevirapine, and combining multiple different ARV prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many studies include single-dose

nevirapine combined with another ARV, usually zidovudine, as two-drug HIV prophylaxis. Most do not report whether nevirapine was administered at the recommended prophylaxis dose or at a higher dose as part of empiric HIV therapy. So, despite increasing use of various ARV prophylaxis regimens, comprehensive data on efficacy and safety are lacking. For newborns at higher risk of HIV acquisition (Table 11), the Panel recommends the NICHD-HPTN 040/PACTG 1043 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine as an option for management.

Empiric HIV Therapy

The other option that the Panel recommends for newborns at higher risk of perinatal acquisition of HIV is a three-drug ARV empiric HIV therapy regimen consisting of zidovudine, lamivudine, and either nevirapine (at treatment dosage) or raltegravir.

Enthusiasm for the three drug approach followed a case of a "functional cure" of HIV in an newborn reported in 2013.[21] The newborn was born by vaginal delivery at 35 weeks' gestation to a woman who received no prenatal care and whose HIV infection was diagnosed by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. When the newborn was 30 hours old, a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher treatment dose rather than standard prophylactic dosing) was initiated. The newborn was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these test results, the newborn was continued on treatment for HIV, thought to be acquired *in utero*. At age 18 months, the mother discontinued the child's ART; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for >2 years without ART. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest is the subsequently reported case of an infant treated from birth and virologically suppressed for 4 years who had virologic rebound within days of ART discontinuation.[22]

Further support of empiric HIV therapy comes from Canadian investigators who have reported outcomes in 136 newborns considered at higher risk of HIV acquisition (i.e., born to women with HIV who had detectable viral loads and/or poor adherence to therapy prior to delivery) who received a triple-ARV regimen within 72 hours of birth. Of these 136 newborns, 12 (9%) were found to be have acquired HIV and no major regimen-related toxicities were identified.[23] However, there was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug regimens. Another Canadian study compared the safety of empiric HIV therapy in 148 newborns with high-risk exposure (i.e., incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) to zidovudine alone in 145 low-risk newborns in a control group. Thirteen newborns in the empiric HIV therapy group acquired HIV, including five with a positive HIV NAT within the first 48 hours of life, suggesting *in utero* infection. No newborn in the low-risk zidovudine-only group acquired HIV. Non-specific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects were reported among the newborns receiving empiric HIV therapy but not among those receiving zidovudine only (10.2% vs. 0%, $P < 0.001$). ARV drugs were also more likely to be discontinued prematurely in the newborns receiving empiric HIV therapy than in those receiving only zidovudine (9.5% vs. 2.1%, $P = 0.01$).[24]

Empiric HIV therapy in newborns is consistent with the Centers for Disease Control and Prevention's recommendations for occupational and non-occupational HIV post-exposure prophylaxis in adults, circumstances in which the risk of infection is often lower than for newborns at higher risk of HIV acquisition.[25,26] The use of empiric HIV therapy in newborns was limited until the availability of new PK and safety information about ARVs in the neonatal period. Although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels are ≥10-fold lower than targeted therapeutic levels. However recent studies of therapeutic dosages of nevirapine and raltegravir have established safe doses that achieve targeted PK parameters.[27-31]

At this time, if an empiric HIV therapy regimen is selected, the Panel recommends a combination of zidovudine, lamivudine, and nevirapine (treatment dosage) or zidovudine, lamivudine, and raltegravir (see Tables 11 and 12). The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if returned birth NAT results are negative, while others would continue empiric HIV therapy for 6 weeks depending on risk for HIV transmission. In all cases, zidovudine should be continued for 6 weeks. Consultation with an expert in pediatric HIV to select a therapy duration based on case-specific risk factors and interim HIV NAT results is recommended.

Newborns Born to Mothers with Unknown HIV Status at Presentation in Labor

Expedited HIV testing is recommended during labor for women with unknown HIV status and, if not performed during labor, as soon as possible after birth for the mothers and/or their newborns (see Identification of Perinatal Exposure). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should be immediately initiated on a multi-drug ARV prophylaxis regimen or empiric HIV therapy**, 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, as there is variability in the HIV testing allowed without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should stop breastfeeding 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.[32]

Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus

The optimal ARV regimen for newborns delivered by women with ARV drug-resistant virus is unknown. It is also unknown whether resistant virus in the mother increases the risk of HIV acquisition by the infant. 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 (888-448-8765). However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Data from the WITS study suggest that, in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted.[33,34] Thus, the selection of the newborn ARV regimen should be based on other risk factors (Table 11).

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.[34] However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.[35-39]

Newborns with HIV Infection

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT results meant that neonatal infections were generally not diagnosed in 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. A positive HIV NAT must be repeated to confirm HIV. However, most Panel members do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given the low likelihood of a false-positive HIV NAT.

However, evidence that very early treatment (before age 2 weeks) will lead to prolonged remission or better outcomes in newborns with HIV is lacking. Earlier diagnosis of HIV in newborns and the increasing use of empiric HIV therapy in newborns at higher risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although 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 nevirapine (see Pediatric Antiretroviral Drug Information).

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

- From birth in term and preterm newborns: zidovudine, lamivudine, nevirapine

- From birth in term newborns: emtricitabine, raltegravir

- From age 2 weeks in term newborns: lopinavir/ritonavir (LPV/r)

Dosing recommendations for *premature* newborns are available for zidovudine, lamivudine, and nevirapine only. Neonatal dosing advice, including for premature newborns, is summarized in Table 12. For more detailed information about neonatal dosing recommendations and considerations of these drugs, please see the Pediatric Antiretroviral Drug Information.

Newborns of Mothers Diagnosed with HIV while Breastfeeding

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding 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 women with confirmed HIV in the United States, including those receiving ART (see Guidance for Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed).[40]

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.[41] Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than are those whose mothers have chronic HIV infection[42] because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.[43]

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 post-exposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance than with other non-occupational exposures because the exposure to breast milk is likely to have occurred during a prolonged period rather than a single exposure to the virus.[44]

Several studies of newborns breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn nevirapine, lamivudine, LPV/r, or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.[45-49] No trials have evaluated the use of multi-ARV regimens to prevent transmission after cessation of breastfeeding in mothers with acute HIV infection.

Given the higher risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some Panel members would be to offer empiric HIV therapy until infant HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of empiric HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.[44] As in other situations, decisions regarding ARV management should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks

and benefits of this approach. The National Perinatal HIV Hotline (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Newborns should be tested for HIV prior to initiation of empiric HIV therapy, 4 to 6 weeks and 4 to 6 months after diagnosis of maternal HIV infection and cessation of breastfeeding to determine their HIV status. An additional virologic test should be performed 2 to 4 weeks after discontinuation of empiric HIV therapy (see Diagnosis section). If a newborn is already receiving an ARV prophylaxis regimen other than empiric HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV initiated. Resistance testing should be performed, and the ART regimen modified if needed (see the Pediatric Antiretroviral Guidelines).

Short-Term Antiretroviral Drug Safety

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

Other than zidovudine, lamivudine is the NRTI with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1[13,50,51] or 2 weeks.[5] Six weeks of newborn zidovudine/lamivudine exposure has also been reported. These studies suggest that hematologic toxicity may be greater with zidovudine/lamivudine than with zidovudine 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 severe anemia and neutropenia were observed in newborns exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort of newborns exposed only to maternal and newborn zidovudine. Anemia was reported in 15% and neutropenia in 18% of newborns exposed to zidovudine/lamivudine, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.[52] Similarly, in a Brazilian study of maternal antepartum and 6-week newborn zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of newborns.[53]

Experience with other NRTI drugs for neonatal prophylaxis is more limited.[54,55] Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than to a single NRTI.[52,56-59]

In rare cases, chronic multiple-dose nevirapine prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.[60] These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding newborns receiving nevirapine prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.[5,45-47,49,61]

The Food and Drug Administration (FDA) recently approved infant dosing of raltegravir for term neonates ≥37 weeks gestation at birth and weighing ≥2 kg. Dosing information is not available for preterm or low birthweight infants. Infant raltegravir dosing needs to be increased at 1 week and 4 weeks of age. Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for albumin binding sites, and extremely elevated neonatal plasma raltegravir concentrations could pose a risk of kernicterus.[62] IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates exposed to HIV and who are at risk of acquiring perinatal HIV-1-infection, with or without *in utero* raltegravir exposure. Daily raltegravir 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. There were no drug-related

clinical adverse reactions observed and only three laboratory adverse reactions: one case of Grade 4 transient neutropenia in an infant receiving zidovudine-containing regimen; and two cases of bilirubin elevations (one each, Grade 1 and Grade 2) that were considered non-serious and did not require specific therapy[63] (see Pediatric Antiretroviral Drug Information for additional information).

The safety and PK data about daily dosing from P1110 are from raltegravir-naive infants whose mothers did not receive raltegravir; data collection from infants born to mothers who were receiving raltegravir is ongoing. However, the Panel believes that the FDA-approved dosing of raltegravir, delaying the first dose for infants born to mothers who received raltegravir, is reasonable based on current data about clearance of the drug in premature and raltegravir-exposed infants.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended given the lack of dosing and safety information. In addition, LPV/r oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) started on LPV/r from birth, developed heart block that resolved after drug discontinuation.[64,65] In studies of adults, both ritonavir and LPV/r cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of LPV/r in the neonatal period, an association not found with zidovudine. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to LPV/r *in utero* than in those exposed only in the neonatal period. Term newborns were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.[66] On the basis of these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity,[67] predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of ≥14 days.[68] However, a recent study (ANRS 12174) randomized 1,273 newborns, 615 assigned to LPV/r and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life and only newborns >2 kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that LPV/r is safe in term newborns, 7 days of age and older.[69] At this time, the Panel does not recommend the use of LPV/r before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days.

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Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV (Last updated April 16, 2019; last reviewed April 16, 2019)

Panel's Recommendations
• All adolescents should receive maximally suppressive antiretroviral therapy (ART); this is urgent for those who are sexually active, considering pregnancy, or pregnant **(AII)**.
• ART regimen selection should include consideration of the adolescent's individual needs and preferences **(AIII)**.
• 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 ART 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)**.
• All adolescents living with HIV should be screened for mental health disorders and substance use disorders **(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

The majority of individuals in the United States who acquired HIV through perinatal transmission are now adolescents or young adults; only about <20% are aged <13 years.[1] Most have had a long clinical course with an extensive antiretroviral treatment (ART) history.[2,3] Many older youth and adults initially received nonsuppressive monotherapy or dual-therapy prior to the availability of fixed-dose combination (FDC) regimens. Challenges that affect the treatment of adolescents with perinatally acquired HIV include extensive drug resistance, complex regimens, the long-term consequences of HIV and ART exposure,[4] unfavorable socioeconomic circumstances, and psychosocial factors.[5-8]

In the United States, most adolescents aged ≥14 years who recently received HIV diagnoses acquired their infection by horizontal, rather than perinatal, transmission.[9] They generally follow a clinical course similar to that of adults, and the Adult and Adolescent Antiretroviral Guidelines should be used for treatment recommendations. Additional information that is specific to the care of post-pubertal adolescents can be found in Adolescents and Young Adults with HIV.[10]

Dosing of Antiretroviral Therapy for Adolescents Living with HIV

Puberty is a time of somatic growth and sexual maturation, with females developing more body fat and males more muscle mass. These physiologic changes may affect drug pharmacokinetics (PKs), which is especially important for medications (e.g., the protease inhibitor [PI] atazanavir) that have a narrow therapeutic index and that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.[11]

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some PIs) are administered to children at higher body weight-based or body surface area-based doses than would be predicted by direct extrapolation of adult doses. These doses are based on reported PK data that indicates more rapid drug clearance in children than in adults. TDF should only be

used in patients with certain sexual maturity ratings (SMRs, formerly Tanner staging), due to concerns about associated toxicity.

Timing and Selection of Antiretroviral Therapy

All individuals who are living with HIV, including adolescents, should initiate ART as soon as possible. Recommendations for doses to use when initiating therapy in adolescents whose SMRs are between 1 and 3 can be found in Appendix A: Pediatric Antiretroviral Drug Information and What to Start. Recommendations for initial therapy for adolescents and young adults whose SMRs are between 4 and 5 are available in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. These recommendations reflect the results from two key randomized controlled trials in adults (START and TEMPRANO). These studies demonstrated that the clinical benefits of ART are greater when ART is started early, when a patient's pre-treatment CD4 T lymphocyte (CD4) count is >500 cells/mm^3, than when ART is initiated at a lower CD4 cell count threshold.[12,13] Clinicians who are treating adolescents of childbearing potential should consider some 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).

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 should be assessed regularly. The adolescent's individual needs and preferences should also 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 living with HIV, who are frequently inexperienced with managing their own health care and may lack health insurance. Many are also at risk for mental health issues, including psychiatric, behavioral, and substance use disorders that may interfere with their adherence.[14,15] Compared with adults, these youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.[16-18] 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.[4]

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternatives to changing ARV therapy can include, but are not limited to: simplifying treatment to a once-daily regimen or an FDC tablet, using cell phone alerts and other eHealth approaches to remind patients about taking their medication and attending clinic visits, initiating a short-term deferral of treatment until adherence improves or while adherence-related problems are aggressively addressed, initiating an adherence testing and training period in which a placebo (e.g., vitamin pill) is administered, scheduling appointments more frequently, employing directly observed therapy, and avoiding any regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient's clinical and laboratory status should be monitored carefully while using any of these interventions.

Mental Health 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 disorder, 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.[14,19-21] The most common conditions include anxiety and behavioral disorders, mood disorders (including depression), and attention deficit hyperactivity disorder. Effectively managing psychiatric comorbidities can improve a patient's adherence to medical care, including ART, and lead to better academic performance and interpersonal relationships.[15,22-24]

Interventions that address mental health problems in youth with perinatally acquired HIV are not well studied, but some studies have evaluated pharmacologic interventions; behavioral modification; and individual, family, and group counselling.[25-27] 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.[28]

Sexually Transmitted Infections in Adolescents

Clinicians should discuss the risk of sexually transmitted infections (STIs) with all adolescents who are living with HIV and screen and treat appropriately. Clinicians should regularly obtain a detailed sexual history for adolescent patients in order 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, since multiple sites of infection are common. Furthermore, a negative assay at a single site does not exclude infection at another site.[29] For a more detailed discussion of STIs, see the most recent Centers for Disease Control and Prevention guidelines,[30] Human Papillomavirus Disease in the Adult and Adolescent Opportunistic Infection Guidelines, and Human Papillomavirus in the Pediatric Opportunistic Infection Guidelines.[31,32] All female adolescents living with HIV who are sexually active should receive gynecologic care, and all adolescents should receive the HPV vaccination.

Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents living 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.[33,34] Providers should regularly assess adolescents' desires to become pregnant or avoid pregnancy (also known as their fertility 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, contraception methods, pre-exposure prophylaxis for partners, and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of secondary HIV transmission, should be discussed regularly (see U.S. Medical Eligibility Criteria for Contraceptive Use).[35] For additional information, readers are referred to the following sections of the Perinatal Guidelines: Preconception Counseling and Care for Women of Childbearing Age Living with HIV and Reproductive Options for Couples in Which One or Both Partners are Living with HIV.[36] The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.[37]

The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for an adolescent female. 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 additional information, please see Teratogenicity in the Perinatal Guidelines.[36] Readers should consult the Recommendations for Use of Antiretroviral Drugs During Pregnancy in the Perinatal Guidelines for information about the selection and management of ARV drugs before and during pregnancy for women with HIV who are of childbearing age (see Table 7). Recent safety concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained dolutegravir should be considered when discussing ART regimen options with female adolescents and their caregivers. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and

in the Perinatal Guidelines (see Teratogenicity and Recommendations for the Use of Antiretroviral Drugs in Pregnancy).

Interactions Between Contraceptives and Antiretroviral Drugs

Women living with HIV can use all available contraceptive methods, including hormonal contraceptives, implantable devices, intrauterine devices, the transdermal patch, and vaginal ring.[36]

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs 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 (see the Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker).[38-40] Integrase strand transfer inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives.[41] For more information about potential interactions between ARV drugs and hormonal contraceptives, please 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 ART (specifically TDF), should not preclude the use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility.

Pregnant Adolescents Living 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 the Perinatal Guidelines).[36] Pregnancy should not preclude the use of optimal therapeutic regimens. Clinicians need to consider maternal and fetal safety as well as the need to prevent perinatal transmission when selecting regimens for pregnant women or women who are planning to become pregnant. See the Perinatal Guidelines[36] for more details about choosing an ART regimen for pregnant women living with HIV, including adolescents, and guidance regarding the use of dolutegravir during pregnancy. Pregnancies have been reported as girls with perinatally acquired HIV enter adolescence and young adulthood.[42,43] Some studies suggest higher rates of adverse pregnancy outcomes, such as small-for-gestational-age infants, among pregnant women with perinatally acquired HIV than among those with horizontal HIV infection, and unplanned pregnancy appears to be a frequent occurrence.[43-45] However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV who are receiving ART appears to be similar to the rate among women on ART who acquired HIV by horizontal transmission.[46-50]

Transition of Adolescents into Adult HIV Care Settings

Facilitating a seamless transition for adolescents living with HIV from their pediatric/adolescent medical home to adult care is important but challenging.[51-53] Many adolescents disengage from care during the transition to adult care, putting them at risk for HIV progression and transmission to partners.[54-56] Pediatric and adolescent providers and their multidisciplinary teams should have a formal written plan in place to transition adolescents to adult care. While 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 his or her parents and/or caregivers. Transition is "a multifaceted, active process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child-focused to the adult-focused health care system."[57] 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 is also 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 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.[58] Providing 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 may be beneficial. In this situation, it may be helpful for a pediatric provider and an adult provider to share joint care of a patient for a period of time.

The adolescent-care provider 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 issues, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration, should also be considered during transition.

Currently, there is no definitive model of transition to adult HIV care, and only a limited number of studies have reported on outcomes following transition, though research in this area is ongoing. Several studies have shown that youth who transitioned into adult care settings had higher rates of attrition from care than those who remained in pediatric/adolescent care; in one U.S. study, only 42% of youth receiving care in an adult clinic remained in care after 12 months compared to 75% of those receiving care in a pediatric clinic. Another multisite study in the United States showed that only 37% of youth had successfully transitioned to adult care after a follow-up period of 9 months.[18,55] A report from the United Kingdom suggests that the mortality rate of adolescents with HIV increases after transition.[23,56] In a report on 50 youth from a Baltimore clinic (31 with non-perinatally acquired HIV and 19 with perinatally acquired HIV), only 50% were retained in care 12 months after transition, although 86% of participants were successfully transitioned and linked to adult care.[54] Another study used surveillance data in New York City to examine the continuum of care for youth with perinatally acquired HIV. Rates of continuous engagement in care and viral suppression were 89% and 67%, respectively, for individuals aged 13 years to 19 years. These rates decreased to 76% and 58% for those aged 20 years to 29 years, underscoring the need to critically examine transition and determine the best mechanisms to optimize the long-term outcomes for youth with perinatal HIV infection.[3] A recent retrospective study from Atlanta reported that, while retention rates were initially high once adolescents entered adult care, they had declined significantly by the second year after transition. Pre-transition viral suppression and shorter linkage time between the pediatric and adult clinic were associated with better outcomes post-transition.[56]

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transition plans and who might benefit most from them.[52,59-66] 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 provider communication between pediatric/adolescent clinics and adult clinics;

- Identifying adult care providers who are experts in providing care to adolescents and young adults;

- Addressing barriers caused by a lack of information, stigma, or disclosure concerns, and discussing the differences between the practice styles of adult clinics and pediatric/adolescent clinics;

- Helping youth develop the skills needed to manage their own 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 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 Living with HIV (Last updated April 16, 2019; last reviewed April 16, 2019)

Panel's Recommendations
• Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again before changing regimens **(AIII)**.
• Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(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 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, as well as subtherapeutic or partial dosing.[1,2] Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of drug resistance to one or more drugs in a given 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] In addition to compromising the efficacy of the current regimen, suboptimal adherence can limit the options for future effective drug regimens in patients who develop multidrug-resistant HIV and 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 living with HIV. A variety of factors—including medication formulation, frequency of dosing, drug toxicities and side effects, child's age and developmental stage, as well as psychosocial, behavioral, and sociodemographic characteristics of children and caregivers—have been associated with nonadherence. However, no consistent predictors of either good or poor adherence in children have been identified.[4-6] Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.[7] 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 the drug regimen, patient and family factors, and the patient-provider relationship.[8,9] The limited availability of once-daily and single-tablet regimens and palatable formulations for infants and young children is especially problematic.[10] Furthermore, infants and children are dependent on others for medication administration; barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal.[11,12] Some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.[13] Adherence may also be jeopardized by social and health issues within a family (e.g., substance abuse, poor physical or mental health,

unstable housing, poverty, <mark>violence</mark>, involvement with the criminal justice system, limited social support).[14,15]

Adherence Assessment and Monitoring

Clinicians should begin assessing potential barriers to adherence and discussing the importance of adherence with patients before therapy is initiated or changed. A comprehensive assessment should be instituted for all children with HIV before initiating or changing an ART regimen. Evaluations should assess social and behavioral factors that may influence adherence by children and their families 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. When assessing readiness and preparing to begin treatment, it is important to obtain a patient's explicit agreement with the treatment plan, including strategies to support adherence. It is also important to alert patients to potential adverse effects 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 clinic visit. Adherence is difficult to assess accurately; different methods of assessment have yielded different results and each approach has limitations.[16-19] Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals on ART (see Plasma HIV-1 RNA [Viral Load] and CD4 Count Monitoring in the Adult and Adolescent Antiretroviral Guidelines). In addition, it can be used as positive reinforcement to encourage continued adherence.[20] Clinicians should use at least one other method to assess adherence in addition to monitoring viral load.[18,21] Table 13 includes commonly employed approaches to monitoring medication adherence.

Strategies to Improve and Support Adherence

If there are concerns about adherence, a patient should be seen and/or contacted frequently (by phone, text messaging, 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, a patient can be contacted weekly, or even daily, if necessary.

Strategies should include simplifying the 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.[13,22,23] The evidence is mixed as to the efficacy of programs that are designed to improve adherence by administering directly observed therapy (DOT), but DOT may still be a useful strategy for some patients.[22,24-28] Table 14 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.[29]

Regimen-Related Strategies

ARV drug regimens for children often require taking multiple pills or unpalatable liquids, each with potential adverse effects (AEs) and drug interactions, in multiple daily doses. To the extent possible, 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 chosen to minimize drug interactions and AEs.[30] Efforts should be made to reduce the pill burden and pill size and to prescribe once-daily ARV drug regimens and single-tablet regimens whenever feasible (see Table 16 in Management of Children Receiving Antiretroviral Therapy). With the introduction of new drug classes and a wider array of once-daily formulations, including some medications that are now available in a small pill size, there are now more options to offer less toxic, simplified regimens, particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-

daily ARV drug regimens than with twice-daily ARV drug regimens, and better adherence with single-tablet formulations than with multiple-tablet regimens.[10,31,32] 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 FDCs in children.

When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can sometimes be masked with a small amount of flavoring syrup or food (see Appendix A: Pediatric Antiretroviral Drug Information).[33] Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children aged 4 years to 21 years found that training children to swallow pills has been associated with improved adherence at 6 months post-training.[34] 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, drug regimen) when feasible.

Patient/Family-Related Strategies

The primary approach to promote medication adherence in children is patient and caregiver education. Educating families about adherence should begin before ARV medications are initiated or changed 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 pillboxes. Additionally, it may be helpful to assess the medication adherence of the caregiver or other household members who are known to be taking 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.[35] Availability of mental health services and the treatment of mental health disorders (such as depression) may facilitate adherence to complex ARV drug regimens.[36,37]

In situations where 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.[38] Therefore, the decision to disclose HIV status should not necessarily be expected to improve adherence. The decision should instead 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, a gastrostomy tube may be considered.[39] If adequate resources are available, home-nursing interventions or DOT may also be beneficial.

Other strategies to support adherence include mobile applications (apps) that remind patients to take medications; setting patients' cell phone 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 (CDC's Every Dose Every Day mobile app) that is available through their website. Several randomized clinical trials in adults have demonstrated an association between text-message reminders and improved adherence[40-44] However, a recent randomized clinical trial in Uganda that involved adolescents and young adults found no difference in electronically measured adherence between participants who received text-message reminders about adherence and those who received standard adherence support.[45] On the other hand, a small study in poorly adherent adolescents and young adults with HIV in the United States demonstrated that two-way personalized daily text messaging improved self-reported adherence.[46] 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.[47-51]

Health Care Provider-Related Strategies

To improve and support 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. 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 establishing links 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) may also better serve more complex patient and family needs, including adherence.

Table 13. Evidence-Based 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 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).
Elicit description of 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 facilitators and challenges to adherence.
Monitor pharmacy refills.	Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to the clinic, home visits, or referral to community health nursing.
Targeted Approaches to Monitoring Adherence in Special Circumstances	**Description**
Implement DOT.	Include brief hospitalization if indicated.
Measure plasma drug concentration.	Measuring plasma drug concentrations can be considered for particular drugs.
Approaches to Monitoring Medication Adherence in Research Settings	**Description**
Measure drug concentrations in hair.	This is a good measure of adherence over time.[19,52,53]
Use electronic monitoring devices.	These include MEMS caps and Wisepill.
Use cell phone-based technologies.	These 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 to Acronyms: apps = applications; 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.
• 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 to arrange for administration in day care, school, and 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 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, reducing 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 management of 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.
• Use patient education aids, including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, mobile apps, alarms, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages 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 are known to 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, such as during a brief 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 to Acronyms: apps = applications; ARV = antiretroviral; AE = adverse effect; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy

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Management of Medication Toxicity or Intolerance <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

Panel's Recommendations
• In children 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 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 side-effect profile should be chosen **(AI*)**.
• The toxicity and the medication presumed responsible should be documented in the medical record 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. However, AEs have been reported 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 (see Adverse Effects of Antiretroviral Agents in the Adult and Adolescent Antiretroviral Guidelines).[1] In recent clinical trials, however, <10% of <mark>ARV-treated patients</mark> had treatment-limiting AEs.[2-11]

The incidence of some longer-term complications of ART (e.g., bone or renal toxicity, dyslipidemia, accelerated cardiovascular disease) may 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.[3,5,7,12,13] To achieve sustained viral suppression over a child's lifetime, both short-term 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 prior 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 (occurring soon after a drug has been administered), subacute (occurring within 1 to 2 days of administration), or late (occurring after prolonged drug administration). For a few ARV medications, pharmacogenetic markers that are 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 hypersensitivity.[14] For selected children aged <3 years who require treatment with efavirenz, an additional pharmacogenetic marker, cytochrome P450 (CYP) 2B6 genotype, should be assessed in an attempt to prevent toxicity (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).[14-18] For agents such as efavirenz, 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 the Management of Medication Toxicity or Intolerance tables. The 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 provide selected references regarding these toxicities in pediatric patients.

As more new ARV drugs are approved for use in children, many of the older ARV drugs **are no longer recommended** because of the toxicities associated with these agents. The following older ARV drugs have therefore been removed from the Management of Medication Toxicity or Intolerance tables:

• Didanosine

• Enfuvirtide

• Fosamprenavir

• Indinavir

• Saquinavir

• Stavudine

• Tipranavir

Information on the toxicities that are associated with these agents can be found in archived versions of the toxicity tables and archived drug sections. Because peripheral nervous system toxicity is primarily associated with some of the older drugs that were removed from the toxicity tables, e.g., didanosine and stavudine, that toxicity table has also been archived.

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 abacavir, symptomatic hepatotoxicity, or 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) can usually 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.

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 antiemetics and antidiarrheal agents for symptom management. CNS AEs are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime, 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.[19,20] In addition, mild rash can be ameliorated with drugs such as antihistamines. Addressing AEs is essential, as 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 resistance.

In patients who experience unacceptable 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.[9,21,22] For mild to

moderate toxicities, changing to a drug with a different toxicity profile may be sufficient, and discontinuation of all therapy may 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, due to the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see Hypersensitivity Reaction, Table 15l) 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 side-effect profiles should be chosen, when possible.[23-26] 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 only permissible for patients whose viral loads are undetectable.

In general, dose reduction is not a recommended strategy for toxicity management, as 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.[27,28] 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 efavirenz, since increased CNS toxicity has clearly been associated with higher levels of efavirenz (see Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information).

To summarize, management strategies for drug intolerance include:

- 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 abacavir for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor for efavirenz-related CNS symptoms).

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

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Global CNS Depression	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	<u>Onset:</u> • 1 day–6 days after starting LPV/r <u>Presentation</u> *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.	Discontinue LPV/r; symptoms should resolve in 1 day–5 days. If needed, reintroduction of LPV/r can be considered once outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).
Neuropsychiatric Symptoms and Other CNS Manifestations	EFV	<u>Onset:</u> • For many symptoms, onset is 1 day–2 days after starting EFV. • Many symptoms subside or diminish by 2 weeks–4 weeks, but symptoms may persist in a significant proportion of patients. <u>Presentation (May Include One or More of the Following)</u> *Neuropsychiatric Symptoms:* • Abnormal dreams • 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 (tremor, dysmetria, ataxia) **Note:** CNS side effects such as impaired concentration, abnormal dreams, or sleep disturbances may be more difficult to assess in children.	Variable, depending on age, symptoms, and assessment method <u>Children:</u> • 24% for any EFV-related CNS manifestations in one case series, with 18% of participants requiring drug discontinuation. • Five of 45 participants (11%) experienced new-onset seizures in one study in children aged <36 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. <u>Adults:</u> • 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.	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 TT genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants) Prior history of psychiatric illness or use of psychoactive drugs	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	If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration >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 expert pharmacologist input).

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	RPV	Onset: • Most symptoms occur in the first 4 weeks–8 weeks of treatment Presentation *Neuropsychiatric Symptoms:* • Depressive disorders • Suicidal ideation • Abnormal dreams/nightmares *Other CNS Manifestations:* • Headache • Dizziness • Insomnia • Somnolence	Adults: • CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (mostly Grade 1). Depressive disorders of all severity grades were reported in 9% of patients. One percent of patients discontinued RPV due to severe depressive disorders. Children: • Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt. • Somnolence was reported in five of 36 children (14%).	Prior history of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.
	RAL	Onset: • As early as 3 days–4 days after starting RAL Presentation: • Increased psychomotor activity • Headaches • Insomnia • Depression • Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)	Children: • Increased psychomotor activity was reported in one child. Adults: • Headache • Insomnia (<5% in adult trials) • Rare case reports of cerebellar dysfunction in adults	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
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	DTG	<u>Onset</u>: • 7 days–30 days after starting DTG <u>Presentation</u> *Neuropsychiatric Symptoms:* • Depression or exacerbation of preexisting depression • Anxiety • Suicidal ideation or attempted/ completed suicide *Other CNS Manifestations (Generally Mild):* • Insomnia • Dizziness • Headache	<u>Children</u>: • CNS symptoms were uncommonly reported in early clinical experience in children and adolescents. <u>Adults</u>: • Exact frequency of neuropsychiatric symptoms is uncertain; there are case reports for four adult patients. Headache, insomnia, and dizziness are common and usually mild, with a rate of 6.1% reported for insomnia in adults. More severe symptoms that require drug discontinuation, including suicidality, are less common, occurring in ≤1% patients in Phase 3 trials, but these severe symptoms are reported with increasing frequency (4% to 10%) in recent post-marketing reports. • Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.	Pre-existing depression or other psychiatric illness Higher frequency of neuropsychiatric symptoms reported when coadministered with ABC; however, evidence is conflicting. UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)	Use with caution in the presence of psychiatric illness, especially depression. Consider morning dosing of DTG.	For persistent or severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists. For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.

Key to Acronyms: ABC = abacavir; ARV = antiretroviral; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; UGT = uridine diphosphate-glucuronosyltransferase

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Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia
(Last updated April 16, 2019; last reviewed April 16, 2019) (page 1 of 2)

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 with TDF than with TAF NNRTIs: • Lower incidence reported with NVP, RPV, and ETR than with EFV	Onset: • As early as 2 weeks to months after beginning therapy Presentation *PIs:* • ↑ LDL-C, TC, and TG *NNRTIs:* • ↑ LDL-C, TC, and HDL-C *NRTIs:* • ↑ LDL-C, TC, and TG	Reported frequency varies with specific ARV regimen, duration of ART, and the specific laboratory parameters used to diagnose lipid abnormalities. 10% to 20% in young children receiving LPV/r. 40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities. Higher abnormal fasting serum lipids have been observed in ART-naive adults who received EVG/COBI/FTC/TAF than in those who received EVG/COBI/FTC/TDF. Increase in serum lipids from baseline has also been noted in adolescents receiving EVG/COBI/FTC/TAF.	Advanced-stage HIV disease High-fat, high-cholesterol diet Lack of exercise Obesity Hypertension Smoking Family history of dyslipidemia or premature CVD Metabolic syndrome Fat maldistribution	Prevention: • Low-fat diet • Exercise • Smoking-prevention counseling • When possible, use ARVs associated with a lower prevalence of dyslipidemia. These include INSTIs and newer PIs (e.g., ATV, DRV). 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) every 6 months–12 months. *Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:* • Obtain nonfasting screening lipid profiles at entry into care and then every 6 months–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 and 8 weeks, and 3 months after starting lipid therapy.	Assess all patients for additional CVD risk factors. Patients living with HIV are considered to be at moderate risk of CVD.[b] ART regimen changes should be considered, especially when the patient is receiving older PIs (e.g., LPV/r) and/or ritonavir boosting. Substituting 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 treatment results with statin therapy. Refer patients to a lipid specialist early if LDL-C ≥250 mg/dL or TG ≥500 mg/dL. If LDL-C is ≥130 mg/dL but <250 mg, or TG is ≥150 mg/dL but <500 mg/dL, a staged treatment approach is recommended by the NHLBI guidelines.[b] • Implement diet, nutrition, and lifestyle management for 6 months to 9 months. Consult with a dietician if one is available. • If a 6-month 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.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia, continued					• If there are minimal alterations in AST, ALT, and CK, monitor every 3 months–4 months during the first year and every 6 months thereafter (or as clinically indicated). • Repeat FLP 4 weeks after increasing doses of antihyperlipidemic agents.	• 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] • 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 receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.

[a] Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and triglycerides 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.

Key to Acronyms: ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; CVD = cardiovascular disease; DRV = darunavir; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FLP = fasting lipid profile; FTC = emtricitabine; 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; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglyceride

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Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 16, 2019; last reviewed April 16, 2019) (page 1 of 2)

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 with ARV agent; generally <15%	Unknown	Instruct patient to take PIs with food. Monitor for weight loss and ARV adherence.	Reassure patient that these adverse effects generally improve over time (usually 6–8 weeks). Consider switching to ARV drugs with smaller tablet sizes (see Appendix A, Table 2). 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 with ARV agent; generally <15%	Unknown	Monitor for weight loss and dehydration.	If prolonged or severe, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea. Reassure patient that this adverse effect generally improves over time (usually 6–8 weeks). Consider switching to another ARV 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: • Dietary modification • 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.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Pancreatitis	Rare, but may occur with RTV-boosted PIs or NRTIs	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% in a recent case series	Use of concomitant medications 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 to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; FDA = Food and Drug Administration; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

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Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 16, 2019; last reviewed April 16, 2019) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Anemia[a]	ZDV	Onset: • Variable, weeks to months Presentation Most Commonly: • Asymptomatic • Mild fatigue • Pallor • Tachypnea Rarely: • Congestive heart failure	Newborns Exposed to HIV: • Severe anemia is uncommon but may be seen 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 compared to all other regimens.	Newborns Exposed to HIV: • Premature birth • *In utero* exposure to ZDV-containing regimens • Advanced maternal HIV • Neonatal blood loss • Combination ARV prophylaxis or empiric HIV therapy, particularly with ZDV plus 3TC Children with HIV Who Are Taking ARV Drugs: • Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency) • Myelosuppressive drugs (e.g., TMP-SMX, rifabutin) • Iron deficiency • Advanced or poorly controlled HIV disease • OIs of the bone marrow • Malnutrition	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 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 Hgb is <7.0 g/dL or is associated with symptoms. • ZDV administration can be limited to 4 weeks in low-risk neonates (see Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). 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 ARV drugs (typically macrocytic anemia), switch to a regimen that does not contain ZDV.
Macrocytosis	ZDV	Onset: • Within days to weeks of starting therapy Presentation: • Asymptomatic but MCV is often >100 fL • Sometimes associated with anemia	All Ages: • >90% to 95%	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.

Adverse Effects	Associated ARVs	Onset/ Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
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-containing regimens	Newborns Exposed to HIV: • *In utero* exposure to ARV drugs • Combination ARV prophylaxis, particularly with ZDV plus 3TC Children with HIV Who Are Taking ARV Drugs: • Advanced or poorly controlled HIV infection • Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)	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 Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV). Children with HIV Who Are Taking ARV Drugs: • Discontinue non-ARV, marrow-toxic drugs, if feasible. • Treat coexisting OIs and malignancies. • For persistent, severe neutropenia that is thought to be associated with ARV drugs, change to a regimen that does not contain ZDV.

[a] HIV infection itself, OIs, and medications used to prevent OIs (e.g., TMP-SMX) may all contribute to anemia and neutropenia.

Key to Acronyms: 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; dL = deciliter; fL = femtoliter; G6PD = glucose-6-phosphate dehydrogenase; Hgb = hemoglobin; MCV = mean cell volume; NRTI = nucleoside reverse transcriptase inhibitor; 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
(Last updated April 16, 2019; last reviewed April 16, 2019) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Hepatitis	Most ARV drugs have been associated with hepatitis, but there is a strong association between hepatitis, NVP, and EFV. NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs. NRTIs have been associated with lactic acidosis and hepatic steatosis, especially ZDV.	Onset: • Acute toxic hepatitis most commonly occurs within the first few months of therapy, but it can occur later. • Steatosis presents after months to years of therapy. • Patients with HBV coinfection may develop flare of hepatitis with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if the patient is receiving only one anti-HBV agent). Note that HBV has a high genetic barrier for resistance to TDF and TAF. • Hepatitis may be a manifestation of IRIS if it occurs early in 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.	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/mm^3 • Male sex with pre-NVP CD4 count >400 cells/mm^3 • Population-specific HLA types[a]	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 months–4 months thereafter;[b] monitor at-risk patients more frequently (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT levels). *For NVP:* • Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.	Evaluate the patient for other infectious and non-infectious 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 permanently discontinued**. • Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.

Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events
(Last updated April 16, 2019; last reviewed April 16, 2019) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Indirect Hyperbilirubinemia	ATV	Onset: • Within the first months of therapy Presentation: • May be asymptomatic or associated with jaundice • Levels of direct bilirubin may 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 receiving ATV had at least one total bilirubin level >5 times ULN and 1.4% of children experienced jaundice.	N/A	Monitoring: • No ongoing monitoring needed. • After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.	Isolated indirect hyperbilirubinemia is not an indication for cessation of the potentially offending ARV drug. Psychological impact of jaundice should be evaluated, and alternative agents should be considered. Jaundice may result in nonadherence, particularly in adolescents; this side effect should be discussed.
Non-Cirrhotic Portal Hypertension	d4T, ddI The Panel **no longer recommends** the use of these agents.	Onset: • Generally after years of therapy; may occur years after stopping therapy. Presentation: • GI bleeding, esophageal varices, and hypersplenism • Mild elevations in AST and ALT levels, moderate increases in ALP levels, and pancytopenia Liver Biopsy Findings: • Most commonly seen findings include nodular regenerative hyperplasia and hepatoportal sclerosis.	Rare	Prolonged exposure to ddI and the combination of d4T and ddI.	Monitoring: • No specific monitoring	Manage complications of GI bleeding and esophageal varices.

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

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

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; EBV = Epstein-Barr virus; EFV = efavirenz; FTC = emtricitabine; GI = gastrointestinal; 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; RTV = ritonavir; 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, Diabetes Mellitus (Last updated April 16, 2019; last reviewed April 16, 2019)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Insulin Resistance, Asymptomatic Hyperglycemia, DM[a]	ZDV, LPV/r, and possibly other PIs	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: • Insulin resistance, 6% to 12% (incidence is higher during puberty, 20% to 30%) • Impaired fasting glucose, 0% to 7% • Impaired glucose tolerance, 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 ARV therapy • 3 months–6 months after therapy initiation • Once a year thereafter *For 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 patient is receiving ZDV, change to TAF, TDF, or ABC. For Either RPG ≥200 mg/dL Plus Symptoms of DM or FPG ≥126 mg/dL: • Patient meets diagnostic criteria for DM; consult an endocrinologist. FPG 100–125 mg/dL: • Impaired FPG suggests insulin resistance; consult endocrinologist. FPG <100 mg/dL: • This FPG is normal, but a normal FPG does not exclude insulin resistance. Recheck FPG in 6 months–12 months.

[a] Insulin resistance, asymptomatic hyperglycemia, and DM form a spectrum of increasing severity.

Insulin Resistance: Often defined as elevated insulin levels for the level of glucose observed.

Impaired FPG: Often defined as an FPG of 100–125 mg/dL.

Impaired Glucose Tolerance: Often defined as an elevated 2-hour PG of 140–199 mg/dL in a 75-g OGTT (or, if the patient weighs <43 kg, 1.75 g per kg of glucose up to a maximum of 75 g).

Diabetes Mellitus: Often defined as either an FPG ≥126 mg/dL, and RPG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1c of ≥6.5%, or a 2-hour PG ≥200 mg/dL after an OGTT.

However, the Panel 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 to Acronyms: ABC = abacavir; ARV = antiretroviral; BMI = body mass index; dL = deciliter; DM = diabetes mellitus; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = lopinavir/ritonavir; OGTT = oral glucose tolerance test; PG = plasma glucose; 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
(Last updated April 16, 2019; last reviewed April 16, 2019)

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 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. *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 multi-organ failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure).	Lactic acidosis is associated with use of ddI and d4T. Cases are rare now that these NRTIs **are no longer recommended**. 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 cell count <350 cells/mm^3 • Acquired riboflavin or thiamine deficiency • Possibly pregnancy Preterm Infants or Any Neonates Who Have Not Attained a Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days: • Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution). A diminished ability to metabolize propylene glycol may lead to accumulation and potential adverse events.	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:* • 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; serum albumin; and hepatic transaminases.	Lactate 2.1–5.0 mmol/L (Confirmed with a Second Test): • Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic workup. 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, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C) Following the resolution of clinical and laboratory abnormalities, resume therapy, either with a 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, or TDF preferred; possibly 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 to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI; didanosine; 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—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated April 16, 2019; last reviewed April 16, 2019) (page 1 of 2)

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: • Trunk and limb fat are the first sign; peripheral fat wasting may not appear for 12 months–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: • Initiating a calorically appropriate, low-fat diet and exercise Monitoring: • BMI measurement • Body circumference and waist-hip ratio	Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs. Improvement in fat maldistribution following a regimen change is variable. 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 are most often 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 in males or breast hypertrophy in females, particularly with the use of EFV.	<5% with current regimens	Obesity before initiation of therapy Sedentary lifestyle	Prevention: • Initiating a calorically appropriate, low-fat diet and exercise Monitoring: • BMI measurement • Body circumference and waist-hip ratio	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). Recommend smoking cessation (if applicable) to decrease future CVD risk. Consider using an INSTI instead of a PI or EFV. 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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
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.	<5% with currently used regimens	Underweight before ART	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 if 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

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; CVD = cardiovascular disease; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

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

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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 in some cases	ATV-related nephrolithiasis occurs in <10% of patients.	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 months–12 months.	Provide adequate hydration and pain control. Consider using another ARV 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 a year of therapy. • Abnormal urine protein/osmolality ratio may be an early indicator. Presentation *More Common:* • Increased serum creatinine, 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	Adults: • Approximately 2% experience increased serum creatinine levels. • Approximately 0.5% experience severe renal complications Children: • Approximately 4% experience hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy and advanced HIV infection.	Risk May Increase in Children with the Following Characteristics: • Aged >6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • Hypertension • Diabetes • Concurrent use of PIs (especially LPV/r) and preexisting renal dysfunction • Risk increases with longer duration of TDF treatment.	Monitor urine protein, urine glucose and serum creatinine at 3-month to 6-month intervals. For patients taking TDF, some Panel members routinely monitor serum phosphate levels. Measure serum phosphate if the patient experiences persistent proteinuria 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.	If TDF is the likely cause, consider using an alternative ARV drug. TAF has significantly less toxicity than TDF.

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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Elevation in Serum Creatinine	DTG, COBI, RPV	Onset: • Within a 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 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.	N/A	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.

Key to Acronyms: ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; dL = deciliter; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; LPV/r = lopinavir/ritonavir; 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 (Last updated April 16, 2019; last reviewed April 16, 2019)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Osteopenia and **Osteoporosis**	Any ART regimen Specific Agents of Concern: • TDF, especially when used in a regimen that includes a boosting agent (i.e., RTV, COBI) • PIs, especially LPV/r	Onset: • Any age; decrease in BMD is usually seen soon after initiation of ART. Presentation: • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma)	BMD z Score Less Than -2.0: • <10% in U.S. cohorts • Approximately 20% to 30% in international cohorts	Longer duration and greater severity of HIV disease Vitamin D insufficiency/deficiency Delayed growth or pubertal delay Low BMI Lipodystrophy Non-black race 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 EFV or an unboosted INSTI. • When using TDF in a regimen, consider supplementing with vitamin D3 at a daily dose of 1,000–4,000 IU Monitoring: • Assess nutritional intake (calcium, vitamin D, and total calories). • Strongly consider measuring serum 25-OH-vitamin D levels, particulary in patients who are taking ARV drugs of concern.[a] • Obtain a DXA.[b]	Same options as for prevention. Consider changing the ARV regimen (e.g., switching from TDF to TAF, and/or from LPV/r to EFV or an un-boosted INSTI whenever possible). Treat patient with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. Vitamin D3 levels should be monitored in patients who are receiving a daily dose of vitamin D3 >4,000 IU. The role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

[a] Some experts periodically measure 25-OH-vitamin D. This is especially important in children and adolescents with HIV who live in urban areas; the prevalence of vitamin D insufficiency is high in that population.

[b] Until more data are available on the long-term effects of TDF on bone mineral acquisition in childhood, DXA scanning is not usually recommended for children who are being treated with TDF. Obtaining a DXA could be considered for adolescent women who are receiving TDF and medroxyprogesterone and for children with indications that are not uniquely related to HIV infection (such as cerebral palsy).

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; COBI = cobicistat; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; IU = international unit; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; 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 (Last updated April 16, 2019; last reviewed April 16, 2019) (page 1 of 4)

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 are 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%):** • LPV/r • MVC • RAL • RPV	Sulfonamide allergy is a risk factor for rash in patients who are taking PIs that contain a sulfonamide moiety (e.g., DRV). Polymorphisms in CYP2B6 and multiple HLA loci may confer an increased risk of rash in patients who are taking NVP.	**When Starting NVP or Restarting After Interruptions of >14 Days:** • Utilize once-daily lead-in dosing.[a] This may not be necessary in children aged <2 years.[b] • Avoid the use of systemic corticosteroids during NVP dose escalation. • Assess 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, 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.	**Infrequent:** • NVP (0.3%) • EFV (0.1%) • ETR (<0.1%) **Case Reports:** • ABC • ATV • DRV • LPV/r • RAL • ZDV	**Adults:** • Female sex • Patients who are black, Asian, or Hispanic are at higher risk.	**When Starting NVP or Restarting After Interruptions of >14 Days:** • Utilize once-daily lead-in dosing.[a] This may not be necessary in children aged <2 years.[b] • Counsel families to report symptoms as soon as they appear.	Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). Provide intensive supportive including care, IV hydration, aggressive wound care, eye care, labial adhesion preventative care, pain management, and antipyretics. 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. When SJS/TEN/EM major occurs with the use of one NNRTI, many experts would avoid the use of other NNRTIs.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
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	Obtain a CBC and AST, ALT, and creatinine levels from a patient who presents with suggestive symptoms.	Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX). The role of systemic steroids in treatment 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 and excluding SJS/TEN	ABC	Onset *With First Use:* • Within first 6 weeks *With Reintroduction:* • Within hours 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.	<1% to 9% (varies by ethnicity)	HLA-B*5701 (HSR is very uncommon in people who are HLA-B*5701 negative). The risk of HSR is higher in patients who are white compared to patients who are black or East Asian.	Screen for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is present.** The medical record should clearly indicate that ABC is **contraindicated**. When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.	Discontinue ARV drugs and investigate other causes of the symptoms (e.g., a concurrent viral illness). 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.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
HSR, continued	NVP	<u>Onset:</u> • Occurs most frequently in the first few weeks of therapy, but can occur through 18 weeks <u>Presentation:</u> • Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy	Occurs in 4% of patients on average, with a range of 2.5% to 11%	<u>Adults:</u> • Treatment-naive with a higher CD4 count (>250 cells/mm^3 in women; >400 cells/mm^3 in men) • Female sex (risk is three-fold higher in females than in males) <u>Children:</u> • NVP hepatotoxicity and HSR are less common in prepubertal children 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, hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages <15%.	<u>When Starting NVP or Restarting After Interruptions of >14 Days:</u> • 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 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.	Discontinue ARV drugs. Consider other causes for hepatitis and discontinue all hepatotoxic medications. Provide supportive care as indicated and monitor the patient closely. Do not re-introduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
HSR, continued	ETR	<u>Onset</u>: • Any time during therapy <u>Presentation</u>: • Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue ARV drugs. Rechallenge with ETR **is not recommended**.
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT levels in patients with rash or other symptoms of hypersensitivity.	Discontinue all ARV drugs. Rechallenge with MVC **is not recommended**.
	DTG	Rash with hepatic dysfunction	Rare	Unknown	Obtain AST and ALT levels in 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 NVP section of the Drug Appendix.

[b] Lead-in dosing **is not recommended** when using nevirapine for either empiric or definitive HIV therapy in newborns with perinatal HIV exposure or perinatal HIV. See the NVP section of the Drug Appendix and Table 12.

Key to Acronyms: ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP = cytochrome P450; 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; 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; 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 <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

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

- <mark>Treatment Simplification:</mark> Modifying ARV regimens in children who are currently receiving effective ART in order to simplify the regimen.
- <mark>Treatment Optimization:</mark> Increasing the treatment potency or barrier to resistance of an effective, but older or potentially fragile, regimen or improving the adverse event profile.
- <mark>Toxicity Management:</mark> Recognizing and managing ARV drug toxicity or intolerance (see Management of Medication Toxicity or Intolerance).
- <mark>Treatment Failure:</mark> 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 regularly evaluated for opportunities to change to a new regimen that facilitates adherence, simplifies administration, increases ARV potency or barrier to resistance, and decreases the risk of drug-associated toxicity **(AII)**.
• <mark>Before making changes to a patient's regimen, clinicians must carefully consider the patient's previous regimens, past episodes of ARV therapy failure, prior drug resistance test results, and the patient's ability to tolerate the new drug regimen **(AIII)**. Archived drug resistance can limit the antiviral activity of a new drug regimen.</mark>
• Children should be carefully monitored after a change in treatment. Viral load measurement is recommended 2 weeks 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

<mark>Clinicians choose initial antiretroviral (ARV) regimens for children with HIV by evaluating the pharmacokinetic, safety, and efficacy data for the drugs that are available in formulations that are suitable for the child's age and weight at the start of treatment.</mark> New ARV 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 where patients have achieved sustained virologic suppression (e.g., suppression for 6 months–12 months) on their current regimen, clinicians should consider switching patients to new ARV regimens in order 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] Often the changes enhance adherence and improve quality of life.[2]

<mark>Treatment Simplification</mark>

<mark>Many children with HIV must initiate treatment with twice-daily dosing, and regimens may include a variety of drug formulations, depending on which formulations are available for a child's age and weight. Clinicians</mark>

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 should also consider a child's antiretroviral therapy (ART) history and resistance test results. Small studies have shown that children who achieve virologic suppression using twice-daily dosing for certain ARV drugs (i.e., abacavir, nevirapine) maintain virologic suppression when they switch from twice-daily regimens to once-daily regimens (see the abacavir and nevirapine drug sections and fixed-dose combinations [FDCs] in Table 1 and Table 2). 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**.[3-5 6,7]

Treatment Optimization

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. Treatment optimization may include improving the potency of regimen, improving a child's growth or other health outcomes, or maximizing palatability. Despite concerns for drug class resistance, the results of the NEVEREST 2 study demonstrated that young children (i.e., those aged <2 years) with virologic suppression who switch from LPV/r to a nevirapine-based regimen can maintain virologic suppression as well as those who continue taking LPV/r, provided that they have good adherence and no baseline resistance to nevirapine.[8,9] In the NEVEREST 3 study, children aged ≥3 years who had a history of exposure to nevirapine and who achieved virologic suppression on a LPV/r-based regimen maintained virologic suppression when switched from LPV/r to an efavirenz-based regimen.[10-12] Similarly, in the NEVEREST 2 study, children who switched to a nevirapine-based regimen showed better immune and growth responses than those who stayed on a LPV/r regimen.[8] Replacing LPV/r with an equally potent protease inhibitor (PI) (e.g., darunavir, atazanavir) or an integrase strand transfer inhibitor (INSTI) (e.g., elvitegravir, raltegravir, dolutegravir) would likely be effective, but these substitutions have not been directly studied in children.

Toxicity Management

Several studies in 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, tenofovir alafenamide, zidovudine, or abacavir; replacing PIs with non-nucleoside reverse transcriptase inhibitors), including improved lipid profiles.[13-17]

Regimens That Are Not Recommended for Use in Children

Dual-therapy and monotherapy PI regimens (darunavir/ritonavir, LPV/r, atazanavir/ritonavir)[18,19] and monotherapy INSTI regimens (dolutegravir)[20,21] have been used to simplify or reduce the toxicity of regimens in adult patients who have sustained virologic suppression, with varying success. These strategies are still being explored, but they are not currently recommended as management strategies in children due to the lack of data.[19,22-25] The FDC of dolutegravir/rilpivirine (Juluca), a nucleoside-sparing, dual-therapy regimen, was recently approved by the Food and Drug Administration 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. 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-drug or four-drug regimens were randomized to either switch to dolutegravir/rilpivirine or to stay on their original regimens. Results from these trials showed similar rates of virologic suppression in both groups (noninferiority) through 48 weeks.[26] There are no equivalent data for this drug combination in pediatric patients. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (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 use of the FDC dolutegravir/rilpivirine (Juluca) in adolescents and children until more data are available.

Potential Antiretroviral Drug Switches in Children with Virologic Suppression

Table 16 contains examples of potential ARV changes in children with sustained virologic suppression on their current regimen for the purposes 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. It is also critical to consider ART history, tolerability, and all prior drug resistance test results in order to avoid choosing new ARV drugs for which archived drug resistance would re-emerge and limit the activity of the regimen.[27-31] The evidence that supports many of these ARV changes is indirect, 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 weeks–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 (page 1 of 3)

Note: 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 only includes information about switching between ARV drugs; **it does not include all the information that clinicians should consider before prescribing these drugs**. Please refer to 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 SMR Requirements	Potential ARV Drug Switch	Comment
NRTIs			
ABC or 3TC Twice Daily	Aged ≥1 year	ABC once daily	See the abacavir[a] and lamivudine sections.
	Aged ≥3 years	3TC once daily	
ZDV, ddI, or d4T[b]	Aged ≥3 months	ABC	Less long-term mitochondrial toxicity. Children aged ≥1 year can take ABC once daily.
	Aged ≥2 years 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. TDF is available in low-strength tablets alone or in combination with FTC.
	Aged ≥2 years Weighing ≥25 kg	TAF[c]	Less long-term mitochondrial toxicity. Once-daily dosing. 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.
NNRTIs			
NVP	Any age (starting at full-term birth) and weighing ≥2 kg	RAL[d]	RAL has potentially greater barrier to resistance than NVP. Both are dosed twice daily in children.
EFV	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 DRV resistance mutations.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.

Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression (page 2 of 3)

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Drug Switch	Comment
NNRTIs, continued			
EFV, continued	Weighing ≥25 kg	DTG	DTG is available as a smaller single-drug tablet or as an FDC, both of which can be dosed once daily if there are no concerns about INSTI resistance. Higher barrier to resistance, which makes it a good choice for patients who have trouble with adherence. See the dolutegravir section for information regarding safety concerns when using DTG in adolescent females of childbearing potential and pregnant adolescents.[e]
	Aged ≥12 years Weighing ≥35 kg	RPV	RPV may improve lipid levels.
PIs			
LPV/r Twice Daily	Any age (starting at full-term birth) and weighing ≥2 kg	RAL[d]	Better palatability. RAL HD can only be given once daily in children weighing >50 kg. Unlike LPV/r, the use of RAL is not restricted to infants with a corrected gestational age of >42 weeks. RAL granules may be difficult to dose for some caregivers.
	Aged ≥3 years Weighing ≥10 kg	EFV	Once-daily dosing. Better palatability. Lower incidence of adverse lipid effects. See the efavirenz section in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about EFV dosing for children aged <3 years.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	Once-daily dosing. ATV/r may improve lipid levels; 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 improve lipid levels. 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 DRV resistance mutations.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥25 kg	DTG	Once-daily dosing if not concerned about INSTI resistance. May be better tolerated, and can be given as an FDC. See the dolutegravir section for information regarding safety concerns when using DTG in female adolescents of childbearing potential and pregnant adolescents.[e]
	Aged ≥12 years Weighing ≥35 kg	RPV	May be better tolerated.
	Aged ≥6 years Weighing ≥25 kg	BIC as Biktarvy[f]	Once-daily dosing. BIC is available as a component of the FDC BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen; pediatric use is investigational in children and adolescents aged 6 years to 18 years.
Other			
Any Multi-Pill and/or Twice-Daily Regimen	Weighing ≥25 kg	EVG/COBI/FTC/TAF (Genvoya)	Once-daily dosing. Single pill. Alignment with adult regimens. Must be taken with food.
	Weighing ≥25 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 information regarding safety concerns when using DTG in female adolescents of childbearing potential and pregnant adolescents.[e]
	Weighing ≥35 kg SMR 4 or 5	EVG/COBI/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.

Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression (page 3 of 3)

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Drug Switch	Comment
Other, continued			
Any Multi-Pill and/or Twice-Daily Regimen, continued	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 ≥6 years Weighing ≥25 kg	BIC/FTC/TAF[f] (Biktarvy)	Once-daily dosing. Single pill. Pediatric use is investigational in children and adolescents aged 6 years to 18 years.
	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 consistent time daily.
	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 information regarding safety concerns when using DTG in female adolescents of childbearing potential and pregnant adolescents.[e]
	Weighing ≥40 kg SMR 4 or 5	EFV/FTC/TDF (Atripla)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults.

[a] 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 for >6 months (24 weeks) on twice-daily ABC, the dose can be changed from twice daily to once daily.

[b] d4T and ddI should be replaced with a safer drug **as soon as possible** because of concerns about long-term adverse effects (see Archived Drugs in Appendix A: Pediatric Antiretroviral Drug Information).

[c] For children and adolescents weighing 25 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, NNRTI, or a boosted PI.

[d] RAL is recommended for twice-daily use in children. Chewable tablets can be used in children weighing ≥11 kg. RAL HD once daily is **only** recommended for virologically suppressed children weighing ≥50 kg.

[e] Because of recent concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained dolutegravir, this drug should be prescribed with caution in female adolescents. Specific recommendations about the initiation and use of DTG in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for the Use of Antiretroviral Drugs in Pregnancy).

[f] Biktarvy has not been approved by the FDA for use in patients aged <18 years, but it is being studied in children and adolescents aged ≥6 years to 18 years. Consultation with a pediatric HIV expert prior to using Biktarvy in children is recommended.[32,33]

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; 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; TFV = tenofovir; ZDV = zidovudine

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Recognizing and Managing Antiretroviral Treatment Failure <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

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, and before changing to a new regimen **(AI*)**.
• 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, with assessment of anticipated ARV activity based on treatment history and past resistance test results **(AII*)**.
• The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay **(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 there is no standardized definition. Clinical failure is defined as the occurrence of new opportunistic infections (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 plasma viral load below the lower level of detection (LLD), 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 therapy occasionally take longer than 6 months to achieve virologic suppression. Because of this, some experts 1) continue the treatment regimen for infants receiving lopinavir/ritonavir (LPV/r)-based therapy if viral load is declining but is still ≥200 copies/mL at 6 months and 2) monitor closely for continued decline to virologic suppression.[1] However, ongoing nonsuppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens—increases the risk

of drug resistance.[2,3]

There is controversy regarding the clinical implications of HIV RNA levels between the LLD and <200 copies/mL in patients on antiretroviral therapy (ART). 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.[4-6] However, some studies in adults have found that multiple viral load measurements of 50 copies/mL to <200 copies/mL may be associated with an increased risk of later virologic failure.[7-9] "Blips"—defined as isolated episodes of detectable low level of plasma viral load (i.e., <500 copies/mL) followed by a return to viral suppression—are common and not generally reflective of short-term virologic failure; they may indicate an increased risk of virologic failure after 12 months to 24 months.[10-12] However, repeated or persistent plasma viral load detection ≥200 copies/mL (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.[6,12-14]

Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.[15] Patients with baseline severe immunosuppression often take more than 1 year to achieve immune recovery (i.e., a CD4 T lymphocyte [CD4] cell count >500 cells/mm^3), even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur.

In cases of poor immunologic response despite virologic suppression, clinicians should first exclude laboratory error in CD4 or viral load measurements and ensure that CD4 values have been interpreted correctly in relation to the natural decline in CD4 cell count over 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 or 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).

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 adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.[16-18] In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 348 children (37%) had CD4 cell counts <500 cells/mm^3 at ART initiation, including 92 (9.9%) who had CD4 cell counts <200 cells/mm^3. After 1 year of virologic suppression, only seven children (1% of the cohort) failed to reach a CD4 cell count ≥200 cells/mm^3 and 86% had CD4 cell counts >500 cells/mm^3. AIDS-defining events were uncommon overall (occurring in 1% of participants), but they occurred both in children who did achieve improved CD4 cell counts and those who did not.[15]

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

In summary, poor immunologic response to treatment can occur. Management consists of confirming that CD4 and virologic tests are accurate, avoiding drugs 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 does not recommend modifying an ART 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 of these cases represent ART failure. IRIS is one of the most important reasons that new or recurrent opportunistic conditions occur, even in cases where virologic suppression and immunologic restoration/preservation are achieved within the first months of initiating ART. IRIS does not mean that ART has failed and does not generally require discontinuation of ART.[19,20] Children who have suffered irreversible damage to their lungs, brain, or other organs—especially during prolonged

and profound pretreatment immunosuppression—may continue to have recurrent infections or symptoms in the damaged organs because the immunologic improvement may not reverse damage to the organs.[21] Such cases do not represent ART failure and, in these instances, children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should also be evaluated to rule out (and, if 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 opportunistic conditions (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.[15] Although such cases are rare, they may represent ART clinical failure and suggest that 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 this strategy are mixed.[22,23]

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:
• Lab error (in CD4 or viral load measurement)
• Misinterpretation of normal, age-related CD4 decline (i.e., the immunologic response is not actually poor)
• Low pretreatment CD4 cell count or percentage
• Adverse effects of using ZDV
• Use of systemic corticosteroids or chemotherapeutic agents
• Conditions that can cause low CD4 values, such as HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis
Poor Immunologic and Clinical Responses Despite Virologic Suppression:
• Lab error
• Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2)
• Persistent immunodeficiency soon after initiation of 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), lungs (e.g., bronchiectasis), cardiac (cardiomyopathy), renal (HIV-related kidney disease)
• A new clinical event due to a non-HIV illness or condition
• A new, otherwise unexplained HIV-related clinical event (treatment failure)

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; ZDV = zidovudine

Management of Virologic Failure

The approach to managing and subsequently treating virologic failure will differ depending on the etiology of the problem. Assessment of a child with suspected virologic failure should include an evaluation of therapy adherence and medication intolerance, confirmation that prescribed dosing is correct (and understood by the child and/or caregiver) for all medications in the regimen, consideration of pharmacokinetic (PK) explanations of low drug levels or elevated and potentially toxic levels, and evaluation of suspected drug resistance (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). While 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 ART regimen. Please see Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV for guidance on assessing adherence and strategies to improve 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 exclude 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 discontinuation of therapy, plasma viral strains may quickly revert to wild type and reemerge as the predominant viral population, in which case resistance testing would fail to reveal drug-resistant virus (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). Resistance can be identified in this situation 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 treatment failure.

Virologic failure of boosted protease inhibitor (PI)-based regimens is frequently associated with no detectable major PI resistance mutations. Virologic suppression may be achieved by continuing the PI-based regimen and implementing adherence-improvement measures.[24,25]

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 tablet taken once daily) while closely monitoring adherence and viral load. In most cases, however, when there is evidence of poor adherence to the current regimen and it is possible that good adherence to a new regimen is unlikely, emphasis and effort should be placed on improving adherence before initiating a new regimen (see Adherence to Antiretroviral Therapy).

Virologic Treatment Failure with Antiretroviral Drug Resistance Identified

After deciding that a change in therapy is needed, 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.[26-30] This process often requires using agents from one or more drug classes that are new to the patient. Substitution or addition of a single drug to a failing regimen is not recommended, because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency due to the presence of drug-resistance mutations that confer cross-resistance within a drug class.

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 must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate the administration of a regimen. Timing of medication administration is particularly important, as this 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.[31]

Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure

Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made by (or in collaboration with) a pediatric HIV specialist. 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. A general strategy for regimen change is shown in Table

18; however, as additional agents are licensed and studied for use in children, newer strategies that are better tailored to the needs of each patient may be constructed.

If a child experiences failure of initial therapy on an NNRTI-based regimen, changing to a PI-based regimen is generally effective. Studies of adults have found no evidence that a regimen that contains a boosted PI and raltegravir produces better outcomes than a regimen that contains a boosted PI and two nucleoside reverse transcriptase inhibitors (NRTIs). Therefore, most children who experience treatment failure on an initial NNRTI-based regimen should be changed to a regimen of a boosted PI plus two NRTIs.[32,33] Limited data support the use of two NRTIs plus an integrase strand transfer inhibitor (INSTI) following the failure of an NNRTI-based regimen.[34,35] A trial in adults who had experienced failure of an initial NNRTI-based regimen reported that dolutegravir had better efficacy and a better safety profile than LPV/r when these drugs were used in a second-line regimen that included at least one active NRTI.

There is concern about using this approach in children (especially when using INSTIs with a lower barrier to resistance, such as raltegravir), because children who experience treatment failure on NNRTI-based regimens often have substantial NRTI resistance.[36] Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. The NNRTIs etravirine and rilpivirine can retain activity against nevirapine-resistant virus or efavirenz-resistant virus in the absence of certain key NNRTI mutations (see below), but etravirine has generally been tested only in regimens that also contain a boosted PI.

If a child experiences initial therapy failure on a PI-based regimen, there are often limited resistance mutations detected;[36,37] in these cases, an alternative PI that is better tolerated and potent can be used. For example, LPV/r-based regimens have been shown to have durable ARV activity in some PI-experienced children.[38-40] Darunavir/ritonavir-based therapy has also been used.[41,42] Based on more limited data, a change to an INSTI-based regimen can be effective, though the barrier to resistance may be less than for a PI-based regimen.[34,43]

The availability of newer drugs in existing 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). As previously discussed, INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI-based regimens or PI-based regimens.[34,43] Raltegravir is the INSTI that has been studied and used most in children, but dolutegravir (see the dolutegravir section for latest age/weight indications) is increasingly appealing for its once-daily administration, small pill size, and higher barrier to development of drug resistance; it also has activity in patients who have experienced treatment failure on raltegravir-based therapy. However, because of recent concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained dolutegravir, this drug should be prescribed with caution in female adolescents (see dolutegravir section). Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Adolescents and Young Adults with HIV and Management of the Treatment-Experienced Patient) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Maraviroc, a CCR5 antagonist, provides a new drug class, but many treatment-experienced children already harbor CXCR4-tropic virus, which precludes its use.[44] Regimens that include an INSTI and a potent, boosted PI plus or minus etravirine have been effective during small studies of extensively ARV-experienced patients with multiclass drug resistance.[45-48] 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 formulation, pediatric and adult dosing, and toxicity, as well as discussions of 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 ARV 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 a fixed-dose combination tablet). Limited data in adults suggest that continuing lamivudine can contribute to suppression of HIV replication,

despite the presence of lamivudine resistance mutations. Continuation of lamivudine can also maintain a lamivudine mutation (184V) that can partially reverse the effects of other mutations that confer resistance to zidovudine, stavudine, and tenofovir disoproxil fumarate.[49-51]

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, and ideally two, additional active agents.

Enfuvirtide has been approved by the Food and Drug Administration (FDA) for use in treatment-experienced children aged ≥6 years, but it must be administered by subcutaneous injection twice daily.[52,53] PK studies of regimens that included two boosted PIs (LPV/r with saquinavir) suggest that PK targets for both PIs can be achieved or exceeded when these drugs are used in combination in children.[54-56] Regimens containing 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.[57] Availability of newer PIs (e.g., darunavir for children aged ≥3 years) and new classes of ARV drugs (e.g., integrase and CCR5 inhibitors) have lessened the need for enfuvirtide, dual-PI regimens, and regimens of four or more drugs. The FDA has recently granted approval for a humanized monoclonal antibody, ibalizumab, that must be infused every 2 weeks in adolescents (those aged >18 years) and adults with multidrug resistance.[58]

Studies of NRTI-sparing regimens in adults with virologic failure and multidrug resistance have demonstrated no clear benefit of including NRTIs in the new regimen.[59,60] One of these studies reported higher mortality in adults who were randomized to receive a regimen that included NRTIs compared to adults who were randomized to receive an NRTI-sparing regimen.[60] 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.

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 AIDS*info* Clinical Trial Search and by consulting a pediatric HIV specialist. Children should be enrolled in clinical trials of new drugs whenever possible.

Pediatric dosing for off-label use of ARV drugs is problematic, because absorption, hepatic metabolism, and excretion change with age.[61] 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.[62]

Off-label use of ARV agents be necessary for children with HIV who have limited ARV 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 is 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 because no combination of currently available agents is active against extensively drug-resistant virus in a patient or because 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 costs. 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, 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.[63] 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 statuses, and the potential to successfully initiate a fully suppressive ART regimen should be reassessed at every opportunity.

The use of NRTI-only holding regimens or a complete interruption of therapy are not recommended. One trial (IMPAACT P1094) randomized children harboring the M184V resistance mutation with persistent nonadherence and virologic failure to continue their nonsuppressive, non-NNRTI-based regimen or to switch to a lamivudine (or emtricitabine) monotherapy holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 cell count (the primary outcome) over a 28-week period. The median age of the participants was 15 years, the median entry CD4 cell count was 472 cells/mm^3, and the median number of interventions that had been used to address nonadherence was four. Only patients in the lamivudine/emtricitabine arm experienced the primary outcome.[64] Although this was a small study (N = 33), it is the only study ever to randomize patients to either continue using nonsuppressive ART or to switch to lamivudine or emtricitabine monotherapy, and it is unlikely that it will be repeated.

Complete treatment interruption has also been associated with immunologic declines and poor clinical outcomes, and it is not recommended (see Considerations About Interruptions in Antiretroviral Therapy).[65,66]

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[a]

Prior Regimen	New Regimen Options[a]
Two NRTIs plus NNRTI	Two NRTIs plus PI
	Two NRTIs plus INSTI
Two NRTIs plus PI	Two NRTIs plus INSTI
	Two NRTIs plus a different RTV-boosted PI
	INSTI plus a different RTV-boosted PI plus or minus an NNRTI and plus or minus NRTI(s)
Two NRTIs plus INSTI	Two NRTIs plus RTV-boosted PI
	DTG[b] (if not used in the prior regimen) plus RTV-boosted PI plus or minus 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).
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	INSTI plus two NRTIs (if NRTIs are fully active)
	INSTI plus two NRTIs plus or minus RTV-boosted PI (if NRTIs are not fully active)
	INSTI plus or minus RTV-boosted PI plus or minus (ETR or RPV) plus or minus NRTI(s) (if there is minimal NRTI activity). Consider adding T-20 and/or MVC if additional active drug(s) are needed.

[a] Clinicians should evaluate a patient's treatment history and drug-resistance test results when choosing an ART regimen in order to optimize ARV drug effectiveness. This is particularly important in selecting the NRTI components of an 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 FTC and 3TC is present, these medications should be continued if the new regimen contains TDF, TAF, or ZDV as the presence of this mutation may increase susceptibility to these NRTIs. **Please see individual drug profiles for information about age limitations (e.g., do not use DRV in children aged <3 years), drug interactions, and dose adjustments when devising a regimen for children with multiclass drug resistance.** 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.

[b] Because of recent concerns about the potential for neural tube defects in infants born to women who conceived while taking regimens that contained dolutegravir, this drug should be prescribed with caution in female adolescents. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Adolescents and Young Adults with HIV and Management of the Treatment-Experienced Patient) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

Key to Acronyms: 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; DRV = darunavir; DTG = dolutegravir; ETR = etravirine; FTC = emtricitabine; 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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Considerations About Interruptions in Antiretroviral Therapy (Last updated April 16, 2019, last reviewed April 16, 2019)

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 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 may also result in temporary ART discontinuation. In resource-limited settings, children might experience interruptions due to drugs being out of stock locally; there may also be gaps in medication availability during the immigration process. Prolonged interruptions of ART can also result from disengagement from care or other social or psychological issues that affect adherence.

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 restart therapy.[1-3] In a retrospective study of 483 children in the ANRS French national pediatric cohort, 42% of participants had treatment interruptions of ≥3 months (median 12.1 months). Interruption was associated with lower CD4 T lymphocyte cell (CD4) percentages after 4 years, even in those who restarted therapy.[4] 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.[5]

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 of time, 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 Living with HIV.

Structured Treatment Interruptions

Scheduled periods during which ART is not given, known as "structured treatment interruptions," were once considered a potential strategy to provide patients with time off ART, potentially reducing toxicity, costs, and drug-related treatment failures. Randomized clinical trials of adults with HIV have demonstrated that structured treatment interruptions are associated with significantly higher morbidity and mortality compared to continuous ART.[6] Current Department of Health and Human Services 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) with virologic suppression on ART were randomized to receive continuous therapy (CT) or to undergo treatment interruption. While there were no

significant differences in rates of adverse events (AEs) between the two groups at 2 years, 19 of 56 (34%) children in the structured treatment interruption arm met CD4 cell criteria to restart therapy between 6 weeks and 42 weeks after interruption, suggesting that only limited additional time off ART was made possible by this strategy.[7,8] The 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 re-initiate treatment based on CD4 cell decline. The median time to the start of continuous ART after interruption was 33 weeks (interquartile range [IQR] 26 weeks–45 weeks) among the infants who discontinued ART after 40 weeks and 70 weeks (IQR 35 weeks–109 weeks) among the infants who discontinued ART after 96 weeks.[9,10] A secondary analysis of neurodevelopmental outcomes at age 5 years did not show any significant differences among the children in the different study arms.[11] However, brain magnetic resonance imaging studies in a subset of participants at 5 years suggested that children whose ART was interrupted had reduced cortical thickness and lower gyrification in some brain regions compared with children who received continuous ART without interruption.[12] In another randomized trial, 12 of 21 infants in the treatment interruption arm met ART restart criteria within 3 months.[13] In summary, while 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 Perinatal HIV).[14,15] However, the "Mississippi infant" had documented viral rebound after 28 months off ART,[16] and there have been additional reports of infants who experienced rebound viremia after stopping ART, despite having undetectable HIV DNA and RNA while on ART.[17,18] Future research might identify treatment strategies and diagnostic tests that enable ART to be safely interrupted in some children. However, at present, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** treatment interruption as a strategy 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 Treatment Strategies

One approach, called short-cycle therapy (SCT), schedules 4-day treatment interruptions, rather than waiting to restart ART after CD4 cell count declines or other AEs occur. In one proof-of-concept study (ATN015), 32 participants (aged 12 years–24 years) underwent short cycles of 4 days on/3 days off ART.[19] Participants had at least 6 months of documented viral suppression (HIV RNA <400 copies/mL) and CD4 counts above 350 cells/mm^3 and were receiving protease inhibitor-based ART. Most participants demonstrated good adherence to the schedule, but 12 participants (37.5%) developed confirmed viral load rebounds >400 copies/mL, and a total of 18 participants (56%) came off study. SCT had no impact on CD4 cell counts.

A more recent study suggests that scheduling shorter periods of time off ART could result in better outcomes. BREATHER (PENTA 16) was a noninferiority trial that randomized 199 children (aged 8 years–24 years) to receive SCT (5 days on/2 days off) or CT.[20,21] To enroll, participants had to be receiving efavirenz plus two nucleoside reverse transcriptase inhibitors, and they had to have been virologically suppressed (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 (viral load >50 copies/mL) (difference -1.2%; 90% CI, -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.[22]

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 3.6 years; both arms had a failure rate of approximately 16%.[23] 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 vs. eight in the CT arm, with primary difference being rate by hospitalizations); however, the arms experienced comparable rates of Centers for Disease Control and Prevention-stage AEs and Grade 3 or 4 AEs. The BREATHER trial suggests that SCT with efavirenz-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 ART regimens, outside of the context of a trial, and over longer periods of time.

Conclusion

Most studies have shown that treatment can only be safely interrupted in children with HIV for short periods of time. Furthermore, treatment interruption yields minimal potential benefits to counterbalance the risks associated with the use of this strategy, and there is a limited amount of long-term follow-up data. The lower toxicity of current antiretroviral agents decreases the potential benefits of treatment interruptions. It is possible that SCT strategies may be safe for some patients, but additional data are needed to support the use of these strategies. At the present time, 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 may be warranted.

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Appendix A: Pediatric Antiretroviral Drug Information

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

Abacavir (ABC, Ziagen) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablet: 300 mg (scored)

Pediatric Oral Solution: 20 mg/mL

Generic Formulations:
   Tablet: 300 mg

Fixed-Dose Combination Tablets:
- [*Epzicom and Generic*] Abacavir 600 mg/lamivudine 300 mg
- [*Triumeq*] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [*Trizivir*] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

Dosing Recommendations

Neonate and Infant Dose:
- Abacavir is not approved for use in infants aged <3 months.

Infant and Child (Aged ≥3 Months) Dose
Oral Solution:
- Abacavir 8 mg/kg twice daily (maximum 300 mg per dose) or abacavir 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of abacavir, initiation with once-daily abacavir is not generally recommended. In older children who can be treated with pill formulations, therapy can be initiated with once-daily administration. In clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts while receiving the liquid formulation of abacavir twice daily, the abacavir dose can be changed from twice-daily dosing to once-daily dosing 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 AM Dose	Twice-Daily PM Dose	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)

Selected Adverse Events
- 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 abacavir. Patients with no prior HLA-B*5701 testing who are tolerating abacavir do not need to be tested.
- Warn patients and parents about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of abacavir**. **Do not re-challenge**.
- Abacavir can be given without regard to food. The oral solution does not require refrigeration.
- When using FDC tablets that contain abacavir, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

Metabolism/Elimination
- Systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.

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

- Abacavir 300 mg twice daily or 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
- This fixed-dose combination (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.

[*Trizivir*] Abacavir/Lamivudine/Zidovudine

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

- One tablet twice daily

- Eighty-two percent of abacavir metabolites are excreted in urine.
- Abacavir requires a dose adjustment in patients with hepatic insufficiency.
- **Do not use** FDCs such as Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDCs) in patients with impaired hepatic function, because the dose of abacavir cannot be adjusted.
- **Do not use** Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDCs) in patients with creatinine clearance <50 mL/min and patients on dialysis, because the dose of lamivudine cannot be adjusted.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- Abacavir does not inhibit, nor is it 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. Abacavir plasma concentrations can decrease when abacavir is used concurrently with the 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. There are currently no recommendations for dose adjustments when coadministering abacavir and one of these boosted PIs.

- Alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) has been shown to interfere with abacavir metabolism by affecting activity of alcohol dehydrogenase and glucuronyl transferase. This interference led to a 41% increase in abacavir area under the curve plasma exposure in adult men with HIV who received abacavir 600 mg daily.[4]

- Abacavir oral solution contains sorbitol, which decreased the exposure of lamivudine 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) that have been observed in approximately 5% of adults and children (the rate varies by race/ethnicity) receiving abacavir. HSR to abacavir is a multi-organ clinical syndrome that is 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, have also been reported. Pancreatitis can occur. HSRs generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of abacavir. If an HSR is suspected, abacavir **should be stopped immediately and not restarted—hypotension and death may occur upon re-challenge**. The risk of an abacavir HSR is associated with the presence of HLA-B*5701 allele; the risk is greatly reduced by not using abacavir in those who test positive for the HLA-B*5701 allele.

- *Rare:* Increased levels of liver enzymes, elevated blood glucose levels, elevated triglycerides (see cardiac 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 an increased risk of myocardial infarction in adults who are currently using abacavir or who have recently used abacavir; however, other studies have not substantiated this finding, and there are no data on cardiovascular risks associated with abacavir use in children.

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

Abacavir is approved by the 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, recommends using abacavir as a component of the NRTI backbone for children weighing ≥3 kg, starting at 4 weeks of age (see WHO Dosages of Antiretroviral Drugs). This recommendation is based on the general principle of using non-thymidine analogues in first-line regimens and thymidine analogues in second-line regimens. This recommendation also takes into account the availability of President's Emergency Plan for AIDS Relief-approved pediatric generic abacavir formulations, including coformulations that include lamivudine, and the cost of ART in resource-limited settings. No systematic safety assessment has been conducted for using abacavir in children weighing <14 kg.

Efficacy

Both the once-daily and twice-daily doses of abacavir have demonstrated durable antiviral efficacy in pediatric clinical trials, and this drug is of comparable efficacy to other NRTIs in children.[6-10]

Pharmacokinetics

Pharmacokinetics in Children

Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that metabolic clearance of abacavir in adolescents and young adults (aged 13 years–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.[11]

The PKs of abacavir 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 abacavir and lamivudine (PENTA 13 [N = 14], PENTA 15 [N = 18], and ARROW [N = 36]).[4,12-15] The data from these three pediatric trials was used to develop a model for abacavir PKs; this model predicted that systemic plasma abacavir exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged ≤12 years.[12-16] These trials, in combination with PK modeling, demonstrated that once-daily abacavir dosing with either the tablet or the liquid formulation provides plasma PK exposures that are comparable to those seen with twice-daily dosing of abacavir at the same total daily dose.[17]

Dosing

Dosing and Formulations

Initially, the recommended dose for pediatric use was abacavir 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 abacavir 600 mg could be safely used in a person weighing 25 kg (i.e., abacavir 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 abacavir 21.5 mg/kg per day to abacavir 22.5 mg/kg per day when treating patients with the tablet formulation.[4] There is no difference in the abacavir plasma C_{max} and AUC for the abacavir liquid formulation compared to the tablet formulation.[18] Doses of liquid abacavir 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 all three abacavir dosing pediatric trials described above,[12-15] only children who had low viral loads and who were clinically stable on the twice-daily dose of abacavir were eligible to change to once-daily abacavir dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical noninferiority of once-daily abacavir (N = 336) versus twice-daily abacavir (N = 333) in tablet form combined with a once-daily or twice-daily lamivudine-based antiretroviral regimen.[8] To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir liquid formulation. In children who can be treated with pill formulations, initiating therapy with once-daily dosing of abacavir at a dose of 16 mg/kg (with a maximum dose of abacavir 600 mg) is recommended. However, in infants and young children who initiate therapy with the liquid formulation of abacavir, twice-daily dosing is recommended. 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 cell counts.

Toxicity

Abacavir has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,[6,7] and less bone and renal toxicity than TDF.[19,20]

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Emtricitabine (FTC, Emtriva) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Pediatric Oral Solution: 10 mg/mL

Capsule: 200 mg

Fixed-Dose Combination Tablets:

- [*Atripla and Generic*] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [*Biktarvy*] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg
- [*Complera*] Emtricitabine 200 mg/rilpivirine 25 mg/TDF 300 mg
- [*Descovy*] Emtricitabine 200 mg/TAF 25 mg
- [*Genvoya*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [*Odefsey*] Emtricitabine 200 mg/rilpivirine 25 mg/TAF 25 mg
- [*Stribild*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TDF 300 mg
- [*Symtuza*] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [*Truvada low-strength tablets*]
  - Emtricitabine 100 mg/TDF 150 mg
  - Emtricitabine 133 mg/TDF 200 mg
  - Emtricitabine 167 mg/TDF 250 mg
- [*Truvada*] Emtricitabine 200 mg/TDF 300 mg

Dosing Recommendations

Neonatal and Infant (Aged 0 to <3 Months) Dose

Oral Solution:

- Emtricitabine 3 mg/kg once daily

Child (Aged ≥3 Months) and Adolescent Dose

Oral Solution:

- Emtricitabine 6 mg/kg once daily (maximum 240 mg per dose). The maximum dose of oral solution is higher than the capsule dose because the oral solution showed 20% lower plasma exposure during pediatric pharmacokinetic analysis.

Capsules (For Patients Weighing >33 kg):

- Emtricitabine 200 mg once daily

Adult Dose

Oral Solution for Those Unable to Swallow Capsules:

- Emtricitabine 240 mg (24 mL) once daily

Capsules:

- Emtricitabine 200 mg once daily

Selected Adverse Events

- Severe acute exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV) and HIV coinfection who discontinue emtricitabine
- Hyperpigmentation/skin discoloration on palms and/or soles

Special Instructions

- Although emtricitabine can be administered without regard to food, there are food requirements for some fixed-dose combination (FDC) tablet formulations that contain emtricitabine.
- When using FDC tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.
- Emtricitabine oral solution can be kept at room temperature, up to 77°F (25°C), if used within 3 months; refrigerate for long-term storage.
- Before using emtricitabine, screen patients for HBV.

[*Atripla and Generic*] Efavirenz/Emtricitabine/TDF

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

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

[*Biktarvy*] Bictegravir/Emtricitabine/TAF

Child and Adolescent (Aged <18 Years) Dose:

- Biktarvy has not been approved by the Food and Drug Administration (FDA) for use in patients aged <18 years.

Child (Aged <6 Years and Weighing <25 kg) Dose:

- There are currently no data available on the appropriate dose of Biktarvy in children aged <6 years and weighing <25 kg.

Child (Aged 6 Years to <12 Years and Weighing ≥25 kg) Dose:

- One tablet once daily. This is an **investigational dose** that has only been studied in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable antiretroviral (ARV) regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

Child and Adolescent (Aged 12 Years to <18 Years and Weighing ≥35 kg) Dose:

- One tablet once daily. This is an **investigational dose** that has only been studied 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 substitutions associated with resistance to the individual components of Biktarvy.

Adult (Aged ≥18 Years) Dose:

- One tablet once daily in antiretroviral therapy (ART)-naive patients. This dose of Biktarvy can also be used to replace the current antiretroviral (ARV) regimen 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 substitutions associated with resistance to the individual components of Biktarvy.
- See the bictegravir section for additional information.

Metabolism/Elimination

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

Emtricitabine Dosing in Patients with Renal Impairment:

- Decrease the dose of emtricitabine in patients with impaired renal function. Consult the manufacturer's prescribing information for recommended dose adjustments.
- Do not use the FDC Atripla in patients with creatinine clearance (CrCl) <50 mL/min or in patients who require dialysis.
- Do not use the FDCs Truvada or Biktarvy in patients with CrCl <30 mL/min. Do not use Truvada in patients who require dialysis.
- Use Complera with caution in patients with severe renal impairment or end-stage renal disease. Monitor frequently for adverse events, because rilpivirine concentrations may increase in patients with severe renal impairment or end-stage renal disease.
- 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.

[*Complera*] Emtricitabine/Rilpivirine/TDF

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

- One tablet once daily in antiretroviral (ARV)-treatment naive patients who have baseline plasma HIV RNA ≤100,000 copies/mL. This dose of Complera can also 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) for at least 6 months with no history of virologic failure or resistance to the individual components of Complera.
- Administer with a meal of at least 500 calories.

[*Descovy*] Emtricitabine/TAF

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

- *Body Weight 25 to <35 kg:* One tablet once daily in combination with other ARV agents, except for protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e., Descovy can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but **not** a boosted PI).
- *Body Weight ≥35 kg:* One tablet once daily 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 can also 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 for at least 6 months with no history of treatment failure and no known substitutions 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 can also 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 substitutions 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 can also 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 substitutions associated with resistance to the individual components of Stribild.

[*Symtuza*] Darunavir/Cobicistat/Emtricitabine/TAF

Child and Adolescent (Aged <18 Years) Dose:

- Symtuza has not been approved by the FDA for use in patients aged <18 years.

Adult (Aged ≥18 Years) Dose:

- One tablet taken once daily with food in ARV-naive patients or in patients who have been virologically suppressed for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

[*Truvada*] Emtricitabine/TDF (FTC/TDF):

Child, Adolescent, and Adult Dose:

Truvada Dosing Table

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

Drug Interactions (see also the Adults and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* **Do not use** emtricitabine in combination with lamivudine, because these agents share similar resistance profiles and lack additive benefit. **Do not use** emtricitabine with combination medications that contain lamivudine or emtricitabine. 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 for each individual component of a fixed-dose combination tablet.

- *Renal elimination:* Emtricitabine may compete with other compounds that undergo renal tubular secretion. Drugs that decrease renal function could decrease clearance of emtricitabine.

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 HIV and hepatitis B virus (HBV) coinfection who switched from regimens that included emtricitabine to regimens that did not include emtricitabine.

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

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

Efficacy and Pharmacokinetics

Comparative Clinical Trials

Studies assessing 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 emtricitabine or lamivudine. Emtricitabine and lamivudine have been considered interchangeable, but data supporting the ability to switch between these two drugs was lacking. Investigators studying the ATHENA cohort compared the efficacy of TDF plus emtricitabine to TDF plus lamivudine when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ARV-naive patients.[1] The adjusted hazard ratio for the virologic failure of lamivudine-containing regimens compared to emtricitabine-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). There was 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 emtricitabine and lamivudine; however, the difference disappeared after adjusting for pill burden.[2] Current evidence suggests that emtricitabine and lamivudine 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 emtricitabine 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 dosage of 240 mg of the emtricitabine liquid formulation. PK results showed that the plasma exposures seen in these children and adolescents were similar to those seen in adults who received emtricitabine 200 mg once daily. Follow-up data extending to Week 96 indicated that 89% of ARV-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 in this trial. PACTG P1021[5] evaluated the use of emtricitabine 6 mg/kg (with a maximum dose of emtricitabine 200 mg/day of the liquid formulation) in combination with didanosine and efavirenz, all given once daily to ARV-naive children aged 3 months to 21 years. Eighty-five percent of children achieved HIV RNA <400 copies/mL, and 72% of children maintained HIV RNA suppression at <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 emtricitabine liquid solution and capsules enrolled 25 children with HIV aged 2 to 17 years.[3] Emtricitabine 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 emtricitabine 6 mg/kg once-daily dose were approximately equivalent to those seen in adults who received the standard emtricitabine 200-mg dose. However, plasma concentrations of emtricitabine after administration of the capsule formulation were approximately 20% higher than those observed after administration of the liquid solution in this small cohort of children.

Pharmacokinetics in Infants

A study in South Africa evaluated the PKs of emtricitabine in 20 infants aged <3 months with perinatal HIV exposure. The participants received a dose of emtricitabine 3 mg/kg once daily for two 4-day courses, separated by an interval of ≥2 weeks.[6] Emtricitabine exposure (area under the curve [AUC]) in neonates receiving emtricitabine 3 mg/kg once daily was within the range of exposures seen in pediatric patients aged >3 months who received the recommended dose of emtricitabine 6 mg/kg once daily and adults who received the once-daily recommended dose of emtricitabine 200 mg. Over the first 3 months of life, emtricitabine 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 emtricitabine 3 mg/kg and whose mothers received a single dose of emtricitabine 600 mg during delivery, the emtricitabine AUC exceeded the AUC seen in adults and older children. However, emtricitabine 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

Liquid emtricitabine has an advantage over liquid lamivudine, since it can be given once daily at ARV initiation while liquid lamivudine needs to be given twice daily at ARV initiation. When pill formulations of lamivudine or emtricitabine are used, they can be administered once daily.

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

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Lamivudine (3TC, Epivir) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

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 Forumlations:
- 100 mg, 150 mg, and 300 mg tablets
- Fixed-dose combination tablet containing lamivudine 150 mg/zidovudine 300 mg

Fixed-Dose Combination Tablets:
- [*Cimduo*] Lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [*Combivir*] Lamivudine 150 mg/zidovudine 300 mg
- <mark>[*Delstrigo*] Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg</mark>
- [*Epzicom*] Abacavir 600 mg/lamivudine 300 mg
- <mark>[*Symfi*] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg</mark>
- [*Symfi Lo*] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg
- <mark>[*Temixys*] Lamivudine 300 mg/TDF 300 mg</mark>
- [*Triumeq*] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- <mark>[*Trizivir*] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg</mark>

Dosing Recommendations

Note: See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12 for information about using lamivudine for the prevention of perinatal HIV transmission.

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

Oral Solution:
- Lamivudine 2 mg/kg twice daily

Infant and Child Dose

Note: In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine **is not recommended**. 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:
- Lamivudine 4 mg/kg twice daily of the oral solution

Selected Adverse Events

- Severe exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV) and HIV coinfection who discontinue lamivudine.

Special Instructions

- Lamivudine can be given without regard to food.
- Store lamivudine oral solution at room temperature.
- Screen patients for HBV infection before administering lamivudine.
- When using FDC tablets, see other drug sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

Metabolism/Elimination

- Dose adjustment required in patients with renal insufficiency.
- FDC tablets should not be used in patients

Aged ≥3 Months to <3 Years:
- Lamivudine 5 mg/kg twice daily of the oral solution (maximum 150 mg per dose)

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

Weighing ≥14 kg and Able to Swallow Pills:
- Weight-band dosing (see table below; dose is approximately lamivudine 5 mg/kg/day twice daily or lamivudine 10 mg/kg once daily)

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

Weight	Twice-Daily AM Dose	Twice-Daily PM Dose	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 scored tablet is the preferred formulation for pediatric patients weighing ≥14 kg who can swallow a tablet.

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 lamivudine (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 counts. Clinicians should choose a reasonable, once-daily regimen using the once-daily dose of lamivudine indicated above (approximately lamivudine 10 mg/kg, with a maximum of lamivudine 300 mg once daily).

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:
- Lamivudine 150 mg twice daily; *or*
- Lamivudine 300 mg once daily

[*Cimduo*] Lamivudine/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

who are on dialysis or who have creatinine clearance <50 mL/min or impaired hepatic function.

Dose:
- One tablet twice daily

[*Delstrigo*] Doravirine/Emtricitabine/TDF

Adult Dose:
- One tablet once daily
- Not studied in children or adolescents (see doravirine section)

[*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

Note: Symfi Lo has not been studied in children (sexual maturity rating [SMR] 1 to 3) and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents with SMRs 1 to 3 weighing ≥40 kg. Therapeutic drug monitoring is suggested by some Panel members 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

[*Triumeq*] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing ≥25 kg) and Adult Dose:
- One tablet once daily
- This fixed-dose combination (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.

[*Trizivir and Generic*] Abacavir/Lamivudine/ Zidovudine

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

- One tablet twice daily

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[a] Epivir HBV oral solution and tablets contain a lower amount of lamivudine than Epivir oral solution and tablets. The amount of lamivudine in the Epivir HBV solution and tablet was based on dosing for treatment of HBV infection in people without HIV coinfection. If Epivir HBV is used in patients with HIV, the higher dose indicated for HIV therapy should be used as part of an appropriate combination regimen.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- Drugs that decrease renal function could decrease clearance of lamivudine.

- **Do not use** lamivudine in combination with emtricitabine, because these drugs have similar resistance profiles and using them together offers no additional benefit.[1] **Do not use** lamivudine with combination medications that contain lamivudine or emtricitabine. 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 fixed-dose combinations.

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 (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

Lamivudine is approved by the Food and Drug Administration (FDA) for the treatment of children aged ≥3 months. It is a common component of most nucleoside backbones.

Considerations for Use

The efficacy and toxicity of lamivudine are equivalent to the efficacy and toxicity of emtricitabine. Liquid emtricitabine has an advantage over liquid lamivudine, since it can be given once daily at antiretroviral (ARV) initiation while liquid lamivudine needs to be given twice daily at ARV initiation. When pill formulations of lamivudine or emtricitabine can be used, they both are administered once daily.

Comparative Clinical Trials

Studies assessing 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) <mark>tenofovir alafenamide (TAF)</mark>, or abacavir, than the more static components, such as emtricitabine or lamivudine. Emtricitabine and lamivudine have been considered interchangeable, but data supporting the ability to switch between these two drugs was lacking. Investigators studying the ATHENA cohort compared the efficacy of TDF plus emtricitabine to TDF plus lamivudine when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ARV-naive patients.[2] The adjusted hazard ratio for the virologic failure of lamivudine-containing regimens compared to emtricitabine-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). There was 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 emtricitabine and lamivudine; however, the difference disappeared after adjusting for pill burden. Current evidence suggests that emtricitabine and lamivudine have equivalent efficacy and toxicity in ARV-naive patients.[3]

Efficacy

Lamivudine has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data have demonstrated the safety of lamivudine 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 lamivudine plus abacavir was superior to zidovudine plus lamivudine or zidovudine plus abacavir in achieving long-term virologic efficacy.[13]

Pharmacokinetics in Infants

Because of its safety profile and availability in a liquid formulation, lamivudine 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 receiving lamivudine affirms that adjusting the dose from lamivudine 2 mg/kg to lamivudine 4 mg/kg every 12 hours at age 4 weeks for infants with normal maturation of renal function provides optimal lamivudine exposure.[14] For infants, the World Health Organization weight-band dosing (which is up to five times higher than the FDA dose) results in greater plasma concentrations than the lamivudine 2 mg/kg dose.[15] In HPTN 040, lamivudine was administered with nelfinavir and 6 weeks of zidovudine according to a weight-band dosing scheme to prevent perinatal transmission during the first 2 weeks of life. All infants weighing >2,000 g received lamivudine 6 mg twice daily and infants weighing ≤2,000 g received lamivudine 4 mg twice daily for 2 weeks. These doses resulted in lamivudine exposure similar to that seen in infants who received the standard lamivudine 2 mg/kg/dose twice-daily dosing schedule for neonates.[16]

Pharmacokinetics of Liquid versus Tablet Preparations

The PKs of lamivudine have been studied after either single or repeat doses in 210 pediatric subjects. Pediatric subjects who received lamivudine oral solution according to the recommended dosage regimen achieved plasma concentrations of lamivudine that were approximately 25% lower than those of adults with HIV who received the oral solution. Pediatric subjects who received lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults who received tablets. In pediatric subjects, the relative bioavailability of lamivudine oral solution is approximately 40% lower than the relative bioavailability of tablets that containing lamivudine, despite no difference in the bioavailability of these two formulations among adults. The mechanisms for the diminished relative bioavailability of lamivudine solution are unknown,[17] but results from a study in adults that compared the PKs of lamivudine solution administered either alone or with increasing concentrations of sorbitol indicates that sorbitol decreases the total exposure of lamivudine solution.[18] Sorbitol is a component of several ARV solutions, 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 lamivudine 5 mg/kg/dose twice daily or lamivudine 10 mg/kg/dose once daily (with a maximum of lamivudine 300 mg administered daily) in children aged ≥3 months would provide exposures similar to those seen in adult patients who received tablet formulations. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend once-daily dosing of lamivudine until a child is aged ≥3 years. However, this new dosing schedule is now reflected included in the lamivudine package insert, even though there are no clinical data from patients who are receiving both lamivudine and sorbitol-containing medications.

Dosing Considerations—Once-Daily versus Twice-Daily Administration

The standard adult dose for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. Population PK data indicate that once-daily dosing of lamivudine 8 mg/kg leads to area under the curve $(AUC)_{0-24h}$ values that are similar to those seen in patients taking lamivudine 4 mg/kg twice daily, but C_{min} values are significantly lower and 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 lamivudine were evaluated in children with HIV aged 2 years to 13 years in the PENTA 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 lamivudine 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC0-24 and clearance values were similar between these two dosing schedules, and most children maintained an undetectable plasma RNA value after the switch. In the ARROW trial, a PK study of 41 children aged 3 years to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC_{0-24h} and good clinical outcome (disease stage and CD4 T lymphocyte [CD4] cell count) after a switch to once-daily lamivudine. Median follow-up time during this study was 1.15 years.[21] ARROW is a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of lamivudine in >600 pediatric patients who had initiated therapy with twice-daily lamivudine and who had been receiving therapy for ≥36 weeks. Median follow-up time during the study was 114 weeks. The viral load suppression and adverse event profiles for once-daily lamivudine were noninferior to those of twice-daily lamivudine.[22]

All four of the studies discussed above only enrolled patients who had a low viral load or who were clinically stable on twice-daily lamivudine before switching to once-daily dosing. Nacro et al. studied a once-daily regimen composed of non-enteric-coated (EC) didanosine, lamivudine, and efavirenz. Fifty-one ARV-naive children in Burkina Faso, ranging in age from 30 months to 15 years, were enrolled in this open-label, Phase 2 study that lasted 12 months.[23] The patients had advanced HIV with a mean CD4 percentage of 9% and a median plasma RNA of 5.51 $\log_{10}$ copies/mL. At the 12-month follow-up visit, 50% of patients had plasma RNA <50 copies/mL and 80% of patients had <300 copies/mL and marked improvements in CD4 percentage. Twenty-two percent of patients harbored multiclass-resistant viral strains. While PK values were similar to those seen during the PENTA and ARROW trials, the study was complicated by the presence of severe immunosuppression and nonclade B virus and the use of non-EC didanosine. In addition, resistance profiles and rates of virologic failure were not separated by age. Therefore, the Panel supports switching from twice-daily to once-daily dosing of lamivudine in children aged ≥3 years who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 cell count. Clinicians should use a 10 mg/kg/dose of lamivudine oral solution or a weight-based dose of lamivudine tablets (neither exceeding lamivudine 300 mg) as part of a reasonable, once-daily regimen.[24] More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of lamivudine can be used effectively to initiate ARV therapy in children.

Lamivudine undergoes intracellular metabolism to reach its active form, lamivudine triphosphate. In adolescents, the mean half-life of intracellular lamivudine triphosphate (17.7 hours) is considerably longer than that of unphosphorylated lamivudine in plasma (1.5–2 hours). Intracellular concentrations of lamivudine triphosphate are equivalent whether given once-daily or twice-daily in adults and adolescents. This supports a recommendation for once-daily lamivudine dosing based on FDA recommendations.[25,26]

World Health Organization Dosing

Weight-band dosing recommendations for lamivudine have been developed for children weighing ≥14 kg and receiving the 150-mg scored tablets.[27,28]

Both emtricitabine and lamivudine have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, and other topics related to opportunistic infections, please see the Pediatric Opportunistic Infections Guidelines.

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Tenofovir Alafenamide (TAF, Vemlidy) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 25 mg[a]

Fixed-Dose Combination Tablets

- [*Biktarvy*] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg
- [*Descovy*] Emtricitabine 200 mg/TAF 25 mg
- [*Genvoya*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg
- [*Odefsey*] Emtricitabine 200 mg/rilpivirine 25 mg/TAF 25 mg
- [*Symtuza*] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg

Dosing Recommendations

[*Biktarvy*] Bictegravir/Emtricitabine/TAF

Child and Adolescent (Aged <18 Years) Dose:

- Biktarvy has not been approved by the Food and Drug Administration (FDA) for use in patients aged <18 years.

Children Aged (<6 Years and Weighing <25 kg) Dose:

- There are no data on the appropriate dose of Biktarvy in children aged <6 years and weighing <25 kg.

Child and Adolescent (Aged ≥6 Years to <12 Years and Weighing ≥25 kg) Dose:

- One tablet once daily. This is an **investigational dose** that has only been studied in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable antiretroviral (ARV) regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

Child and Adolescent (Aged ≥12 Years to <18 Years and Weighing ≥35 kg) Dose:

- One tablet once daily. This is an **investigational dose** that has only been studied in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable antiretroviral (ARV) regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

Adult (Aged ≥18 Years) Dose:

- One tablet once daily in antiretroviral (ARV)-naive patients. This Biktarvy dose can also 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 for at least 3 months with

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 using TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TAF is stopped.
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC (see the emtricitabine, elvitegravir, cobicistat, rilpivirine, darunavir, and bictegravir sections).
- The FDA does not recommend using Genvoya with other ARV drugs, but this FDC has safely been used with darunavir.[1] Descovy can be safely used with cobicistat-boosted or ritonavir-boosted darunavir or atazanavir in patients weighing ≥35 kg.[2]
- **Do not use** Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs that are coformulated with cobicistat.
- 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 rilpivirine.

no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

- See the bictegravir section for additional information.

[*Descovy*] Emtricitabine/TAF

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

- *Body Weight 25 kg to <35 kg:* One tablet once daily in combination with other ARV agents, except for protease inhibitors (PIs) that require a cytochrome P450 3A inhibitor (i.e., Descovy can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but **not** a boosted PI).

- *Body Weight ≥35 kg:* One tablet once daily 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 ARV-naive patients. This dose of Genvoya can also 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 for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

[*Odefsey*] Emtricitabine/Rilpivirine/TAF

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

- One tablet once daily with a meal in ARV-naive patients with HIV RNA ≤100,000 copies/mL. This dose of Odefsey can also be used to replace a current, stable ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.

[*Symtuza*] Darunavir/Cobicistat/Emtricitabine/TAF

Adult (Aged ≥18 Years) Dose:

- One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

Metabolism/Elimination

- TAF undergoes renal excretion.

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 25-mg tablet[a] **is not recommended** for use in patients with estimated creatinine clearance (CrCl) <15 mL/min. TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl <30 mL/min.

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[a] TAF 25-mg tablets (Vemlidy) are approved by the FDA 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.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [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 in 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 and dolutegravir did not change either TAF or TFV exposure. Coadministration of TAF with the P-gp and BCRP inhibitor cobicistat, or coadministration with atazanavir/ritonavir or lopinavir/ritonavir, increased both TAF and TFV exposures. Coadministration of TAF with darunavir/ritonavir (DRV/r) resulted in unchanged TAF AUC and a doubling of TFV AUC. Coadministration of TAF with the P-gp and BCRP inducer efavirenz decreased TAF and TFV exposures.[3]

- Coadministration of TAF with rifamycins **is not recommended**.[4]

- Genvoya contains [elvitegravir](#) and [cobicistat](#) in addition to TAF. Elvitegravir is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, and by oxidative metabolism pathways. Elvitegravir is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits 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 elvitegravir and cobicistat.

- *Absorption:* Administering elvitegravir and bictegravir concurrently with antacids lowers plasma concentrations of these ARV drugs. This is due to formation of complexes in the gastrointestinal tract, and not because of changes in gastric pH. Chelation by high concentrations of divalent cations, such as calcium or iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and bictegravir. Because of this, Genvoya or Biktarvy should be administered at least 4 hours before or after antacids and iron, calcium, aluminum, and/or magnesium-containing supplements or multivitamins. The Food and Drug Administration (FDA) product label should be consulted for exact recommendations on the timing of dosing for each drug.

- Odefsey contains [rilpivirine](#), 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, and high-dose nonsteroidal anti-inflammatory drugs) could reduce clearance of TAF or emtricitabine. 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, because cobicistat and ritonavir have similar effects on CYP3A metabolism.

Major Toxicities

- *More common:* Nausea, diarrhea, headache.

- *Less common (more severe):* Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of nucleoside reverse transcriptase inhibitors (NRTIs).

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

Descovy, a fixed-dose combination (FDC) drug that contains emtricitabine and TAF (FTC/TAF), is approved by the FDA for use in children aged ≥6 years who weigh ≥25 kg (but <35 kg) when used as part of an ARV therapy regimen that does not include a ritonavir-boosted or cobicistat-boosted protease inhibitor (PI). Descovy is approved by the FDA for use in children aged ≥6 years who weigh ≥35 kg when used in combination with any ARV drugs, including ritonavir-boosted or cobicistat-boosted PIs. Odefsey, an FDC that contains emtricitabine, rilpivirine, and TAF (FTC/RPV/TAF), is approved by the FDA for use in children who weigh ≥35 kg. Genvoya, an FDC that contains elvitegravir, cobicistat, emtricitabine, and TAF (EVG/COBI/FTC/TAF), is approved by the FDA for use in children aged ≥6 years who weigh ≥25 kg when used as the single-tablet regimen without other ARV drugs (see Table A). Bictegravir is only available as part of the FDC Biktarvy, which contains bictegravir, emtricitabine, and TAF (BIC/FTC/TAF). Biktarvy is not approved by the FDA for use in children or adolescents, but it has been studied in adolescents aged 12 to <18 years who weigh ≥35 kg[5] and in children aged 6 to <12 years who weigh ≥25 kg.[6] Symtuza, an FDC that contains darunavir, cobicistat, emtricitabine, and TAF (DRV/COBI/FTC/TAF) is approved by the FDA for use in adults.

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, there could be rebound of clinical hepatitis when TAF is stopped. For more information about hepatitis rebound in patients with HBV/HIV coinfection, see the Pediatric Opportunistic Infection Guidelines. TAF alone (as Vemlidy) is approved by the FDA for use in persons aged ≥8 years, and it is only approved for treating HBV, not HIV.

Formulations

TAF-containing pills are smaller than their tenofovir disoproxil fumarate (TDF)-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills. TAF is available as the coformulated tablets FTC/TAF (Descovy),[2] FTC/RPV/TAF (Odefsey),[7] EVG/COBI/FTC/TAF (Genvoya),[8] BIC/FTC/TAF (Biktarvy),[9] and DRV/COBI/FTC/TAF (Symtuza). EVG/COBI/FTC/TAF contains TAF 10 mg while FTC/TAF, FTC/RPV/TAF, and BIC/FTC/TAF contain TAF 25 mg. Cobicistat boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, administration of EVG/COBI/FTC/TAF, which contains TAF 10 mg and cobicistat, achieves TFV-DP systemic exposure that is similar to the exposure achieved by FTC/RPV/TAF or BIC/FTC/TAF, which contain TAF 25 mg but no cobicistat.

Table A. Food and Drug Administration-Approved, Tenofovir Alafenamide-Containing Formulations

Drug	Contains	Dose of TAF	Minimum Age	Minimum Body Weight	Comment
Vemlidy	TAF	25 mg	18 years	N/A	Approved for HBV treatment only.
Descovy	FTC/TAF	25 mg	6 years	25 kg	Use with an INSTI or NNRTI, but **not** with a boosted PI.
	FTC/TAF	25 mg	6 years	35 kg	Use with any ARV drugs, including a boosted PI.
Odefsey	FTC/RPV/TAF	25 mg	12 years	35 kg	**Not to be used with other ARV drugs.**
Genvoya	EVG/COBI/FTC/TAF	10 mg	6 years	25 kg	TAF dose is lower because of the COBI boosting.
Biktarvy[a]	BIC/FTC/TAF	25 mg	18 years	N/A	**Not to be used with other ARV drugs.**

[a] See the Bictegravir section for information about the investigational use of this drug in children and adolescents aged 12 years to 18 years who weigh ≥35 kg.

Key to Acronyms: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; EVG = elvitegravir; 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[10,11] 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).[12] 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[13] also has good oral bioavailability.[14] 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.[15] Once inside the cell, TAF is hydrolyzed to TFV,[16,17] 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.[13] Therefore, a much lower dose of TAF results in intracellular concentrations of TFV-DP that are equivalent to or higher than the concentrations seen after TDF administration.

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 and therapeutically effective intracellular TFV-DP concentrations.[15,18] Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy equivalent to TDF. However, the toxicities that are specifically related to plasma TFV 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).[19] High plasma TFV has also been closely associated with both glomerular[19-21] and proximal tubular[22] renal toxicity.

Table B. Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV:[a] Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate[b]

Parameter	TAF 8 mg (N = 9)	TDF 300 mg (N = 6)
Plasma TFV AUC_{tau} (ng•h/mL)	65.5 (23.5)	1,918.0 (39.4)
Plasma TFV C_{max} (ng/mL)	4.2 (24.7)	252.1 (36.6)
Plasma TFV C_{tau} (ng/mL)	2.1 (33.8)	38.7 (44.7)
PBMC TFV-DP AUC_{tau} (µM•h)	3.5 (77.1)	3.0 (119.6)

[a] The mean age of participants was 38 years, with a range of 20 to 57 years.

[b] 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.

Note: Data are mean (% coefficient of variation), tau is the dosing interval (i.e., 24 hours), and C_{max} is the maximum concentration.

Key to Acronyms: AUC = area under the curve; 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 elvitegravir, cobicistat, and emtricitabine;[23-26] with emtricitabine and rilpivirine;[27] with darunavir, cobicistat, and emtricitabine;[28-30] and when TAF and emtricitabine are administered in combination with other ARV drugs.[31] In a switch study of adults who were virologically suppressed on a three-drug regimen that included abacavir, FTC/TAF was noninferior to a regimen of lamivudine plus abacavir plus a third ARV drug over 48 weeks. There were no differences 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 while the abacavir group had an increase in HDL cholesterol levels (-2 mg/dL vs. +2 mg/dL, respectively; *P* = 0.0003).[32] Viral load suppression was attained in about 90% of study participants when TAF was given as part of the coformulated, single-tablet regimen BIC/FTC/TAF.[33-35]

Tenofovir Alafenamide Efficacy in Clinical Trials in Adolescents and Children

The combination of TAF, elvitegravir, cobicistat, and emtricitabine has been shown to have similar efficacy when used in adults and two groups of children: those aged ≥12 years and weighing ≥35 kg[36] and those aged ≥6 years and weighing ≥25 kg.[37] In one study, treatment with the single-tablet regimen BIC/FTC/TAF resulted in

Pharmacokinetics

Drug Exposure and Virologic Response

Virologic suppression is most closely related to intracellular TFV-DP concentrations. At clinically meaningful doses, TAF generates peripheral blood mononuclear cell TFV-DP concentrations in adults that are two-fold[18] to seven-fold higher than those generated with TDF.[15,23] Higher TFV-DP concentrations result in a stronger antiviral potency[15] and a higher barrier to resistance.[38,39] Therefore, since 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 youths aged 12 years 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.[36]

Drug Exposure and Safety: All Age Groups

FTC/TAF can be safely combined with dolutegravir or raltegravir without concern for drug interactions. Emtricitabine and TAF have also safely been combined with bictegravir in the FDC Biktarvy.

When FTC/TAF, which contains TAF 25 mg, is combined with cobicistat-boosted or ritonavir-boosted atazanavir, darunavir, or lopinavir, the P-gp inhibitors cobicistat or ritonavir increase the TAF exposure to higher concentrations than those seen with use of EVG/COBI/FTC/TAF, which contains TAF 10 mg. However, the plasma TFV concentrations (the cause of bone and renal toxicity) seen with the use of EVG/COBI/FTC/TAF or TAF plus DRV/r or darunavir/cobicistat (DRV/c) are still much lower than those seen with the use of Stribild, an FDC that contains elvitegravir, cobicistat, emtricitabine, and TDF (see Table C).

Table C. Plasma TAF and Plasma Tenofovir Exposures for TAF 10 mg or TAF 25 mg Used in Combination with Boosted Protease Inhibitors

Regimen	TAF AUC[a]	TAF AUC Ratio TAF AUC of TAF-Containing Regimen/ TAF AUC of Genvoya (10 mg TAF) (Adult Exposure)	TFV AUC[a]	TFV AUC Ratio TFV AUC of TAF-Containing Regimen/ TFV AUC of Stribild (300 mg TDF) (Adult Exposure)
Adult				
Stribild (EVG/COBI/FTC/TDF 300 mg)	N/A	N/A	4,400	1.00
Genvoya (EVG/COBI/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/COBI/FTC/TDF 300 mg) for ages 12 years–18 years	N/A	N/A	6,028	1.37
Genvoya (EVG/COBI/FTC/TAF 10 mg) for ages 12 years–18 years	200	0.95	290	0.07
Genvoya (EVG/COBI/FTC/TAF 10 mg) for ages 6 years–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 FDA Summary Review of TAF and from the TAF clinical pharmacology review, using data from the Stribild product label and Genvoya product label.

Key to Acronyms: AUC = area under the curve; COBI = cobicistat; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; EVG = elvitegravir; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

The clinical trials in adults that have shown the safety of emtricitabine plus TAF administered with ritonavir-boosted atazanavir or ritonavir-boosted darunavir have used FTC/TAF 200 mg/10 mg, a formulation not available in the United States.[40] The FDA states that when FTC/TAF 200 mg/25 mg is combined with cobicistat-boosted or ritonavir-boosted atazanavir, darunavir, or lopinavir in adults, "no clinically significant drug interactions have been observed or are expected." The combination of FTC/TAF 200 mg/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 INSTI).[2] Moreover, in Trial 299-0102, 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 compared to the TDF arm.[41] Hence, FTC/TAF 25 mg was recommended for approval instead of FTC/TAF 10 mg.[41] This is not the case in Canada or Europe, where emtricitabine is combined with TAF 10 mg in an FDC for use in combination with boosted PIs.

Drug Exposure and Safety: Aged 12 Years 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/TAF 200 mg/10 mg plus a boosted third ARV drug or FTC/TAF 200 mg/25 mg with an unboosted third ARV drug. The results of this study showed TAF exposures in children and adolescents that were similar to 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 five of 28 participants (18%), and Grade 3 or 4 elevations in fasting low density lipoprotein (LDL) levels were noted in two of 28 participants (7%).[42]

Studies of EVG/COBI/FTC/TAF in children aged 12 years to 18 years and weighing ≥35 kg showed that TAF and TFV exposures were similar to those found in adults (see Table C) and that the drug combination was well tolerated and efficacious over 48 weeks of study.[36] Since these TAF and TFV exposures were similar to those seen in adults, FTC/TAF 200 mg/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 adult-dose formulation of Biktarvy (which contains bictegravir 50 mg, emtricitabine 200 mg, and TAF 25 mg) was administered to youth aged 12 years to <18 years and weighing ≥35 kg and who had had viral loads <50 copies/mL for at least 6 months. The drug was well tolerated, and all 24 participants had viral loads <50 copies/mL at 24 weeks.[5] While the area under the curve (AUC) and C_{max} for bictegravir were similar in adolescents and adults, the mean bictegravir trough in adolescents aged 12 years to <18 years was 2,327 ng/mL (with a CV of 49%); in adults, the mean bictegravir trough was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% CI, 74–100).[5]

BIC/FTC/TAF 50 mg/200 mg/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. Despite a high AUC and C_{max}, the drug combination was well tolerated, with a fall in estimated glomerular filtration rate similar to that seen in adult studies, which is related to changes in tubular secretion of creatinine and not a true change in glomerular function. All 50 participants in the study had viral loads <50 copies/mL at Week 12, and the 26 participants with data up to week 24 likewise all had viral loads <50 copies/mL.[6]

Drug Exposure and Safety: Aged 6 Years to <12 Years and Weighing 25 kg to <35 kg

Studies of EVG/COBI/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), but the drug combination was well tolerated and efficacious over 24 weeks of study.[37,43] This led to FDA approval of EVG/COBI/FTC/TAF for use in children aged ≥6 years and weighing ≥25 kg.[8]

Because integrase inhibitors do not increase TAF concentrations, regimens of FTC/TAF 25 mg plus an INSTI are expected to result in safe drug exposures that are similar to those seen with the single-tablet regimen EVG/COBI/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 cobicistat-boosted or ritonavir-boosted atazanavir, darunavir, or lopinavir increase TAF exposure to concentrations that are higher than those seen with use of EVG/COBI/FTC/TAF, and because there are

no data on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with cobicistat-boosted or ritonavir-boosted PIs in children weighing between 25 kg and <35 kg cannot be assured. That is why the FDA approval for FTC/TAF used in combination with boosted PIs is limited to children weighing ≥35 kg (see Table A).[2]

Dosing: Crushing Emtricitabine/Tenofovir Alafenamide Tablets

There is one report of viral load suppression in a single adult patient with HIV who received crushed FTC/TAF tablets plus crushed dolutegravir 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.[44]

Toxicity

Bone

TAF causes bone toxicity less frequently than TDF.[23-25,28-31,45,46] For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/COBI/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/COBI/FTC/TDF.[23] These differences were maintained to 96 weeks.[26]

Renal

Studies in adolescents aged 12 years to 17 years[36] and adults[23-25,28,29,31] show that TAF is less frequently associated with glomerular and renal tubular damage than TDF. For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/COBI/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/COBI/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.[23] These differences persisted to 96 weeks of follow-up.[26] Safety of EVG/COBI/FTC/TAF has been shown in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.[47] For TAF, less intense renal safety monitoring may be needed than with 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, the initiation of EVG/COBI/FTC/TAF was associated with increases in serum lipids greater than those observed with the initiation of EVG/COBI/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/COBI/FTC/TAF, median changes from baseline to Weeks 24 and 36 were the following: 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.[48] 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.[29] Monitoring serum lipids while the patient is taking TAF-containing FDCs is warranted, given these data. For more information, see the Dyslipidemia section.

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Tenofovir Disoproxil Fumarate (TDF, Viread) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 150 mg, 200 mg, 250 mg, and 300 mg

Oral Powder: 40 mg per 1 g of oral powder (1 level scoop, measured with supplied dosing scoop = 1 g oral powder)

Fixed-Dose Combination Tablets

- [*Atripla and Generic*] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [*Cimduo*] Lamivudine 300 mg/TDF 300 mg
- [*Complera*] Emtricitabine 200 mg/rilpivirine 25 mg/TDF 300 mg
- [*Delstrigo*] Doravirine 100 mg/lamivudine 300 mg/TDF 300 mg
- [*Stribild*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/TDF 300 mg
- [*Symfi*] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg
- [*Symfi Lo*] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg
- [*Temixys*] Lamivudine 300 mg/TDF 300 mg
- [*Truvada low-strength tablet*]
  - Emtricitabine 100 mg/TDF 150 mg
  - Emtricitabine 133 mg/TDF 200 mg
  - Emtricitabine 167 mg/TDF 250 mg
- *[Truvada tablet]* Emtricitabine 200 mg/TDF 300 mg

Dosing Recommendations

Neonate and Infant Dose:
- TDF has not been approved by the Food and Drug Administration or recommended for use in neonates and infants aged <2 years.

Child (Aged ≥2 Years to <12 Years) Dose:[a]
- TDF 8 mg/kg/dose once daily

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)

Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density[a]

Special Instructions

- Do not crush tablets. 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: 1 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

TDF Tablet Dosing Table for Patients Aged ≥2 Years and Weighing ≥17 kg

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

[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 treatment-naive adults with baseline viral loads ≤100,000 copies/mL. This dose of Complera can also be used in virologically suppressed 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 at least 500 calories.

[Delstrigo] Doravirine/Emtricitabine/TDF
Adult Dose:

- One tablet once daily

- Not studied in children or adolescents (see doravirine section)

[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 treatment-naive adults. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV

regard to food, food requirements vary depending on the other ARV drugs contained in a fixed-dose combination (FDC) tablet. Food requirements are listed with dosing recommendations and in Table 2 of the Drug Appendix.

- 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 (see Table 15i) during continued therapy. 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, in patients with HBV infection, monitor hepatic function and hepatitis B viral load for several months after therapy with TDF is stopped.

- When using FDC tablets, see other drug sections for special instructions and additional information about the individual drug components.

- 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

- TDF is renally excreted.

TDF Dosing in Patients with Renal Insufficiency:

- TDF dose should be decreased in patients with impaired renal function (creatinine clearance [CrCl] <50 mL/min). Consult manufacturer's prescribing information for adjustment of dose in accordance with CrCl.

- The FDCs Atripla, Complera, and Symfi Lo should not be used in patients with CrCl <50 mL/min or in patients requiring 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

RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions 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

Note: Symfi Lo has not been studied in children (SMR 1 to 3) and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents SMR 1-3 who weigh ≥40 kg. Therapeutic drug monitoring is suggested by some Panel members 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/TDF 100 mg/150 mg tablet
22 kg to <28 kg	One FTC/TDF 133 mg/200 mg tablet
28 kg to <35 kg	One FTC/TDF 167 mg/250 mg tablet
≥35 kg and Adults	One FTC/TDF 200 mg/300 mg tablet

estimated CrCl <50 mL/min.

- Stribild should not be used in patients with severe hepatic impairment.

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[a] See text for concerns about decreased bone mineral density, especially in prepubertal patients and those in early puberty (SMR 1 or 2).

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [HIV Drug Interaction Checker](#))

- 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).

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations increase when the drug is coadministered with TDF, and this combination **should not be used** because of increase in risk of didanosine toxicity.

- *Protease inhibitors:* Atazanavir without ritonavir **should not be coadministered** with TDF because TDF decreases atazanavir plasma concentrations. In addition, the combination of atazanavir and lopinavir/ritonavir increases plasma TFV concentrations and increases risk of TDF-associated toxicity.[2]

- *Use of Stribild:* If using Stribild, please see the [elvitegravir section](#) of the drug appendix 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 (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

TDF has been approved by the Food and Drug Administration (FDA) for use in children aged ≥2 years when used as a component of antiretroviral therapy (ART).

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is approved by the FDA for HBV treatment in children aged ≥12 years. The use of TDF to treat HBV/HIV coinfection is reviewed in the [Pediatric Opportunistic Infection Guidelines](#).

Efficacy in Clinical Trials in Adults Compared to 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 years to 12 years, the FDA-approved dose is TDF 8 mg/kg/dose administered once daily, which closely approximates the dose of TDF 208 mg/m^2/dose used in early studies in children.[3]

In adults, the recommended TDF 300 mg once daily dose is highly effective. In comparative clinical trials in adults, TDF administered with lamivudine or emtricitabine as a dual-NRTI backbone in combination with efavirenz had better viral efficacy than zidovudine or stavudine administered with lamivudine and efavirenz.[4-6] TDF administered with emtricitabine has been compared to abacavir administered with lamivudine in several

adult studies and meta-analyses, with variable results.[7-11]

The FDA approved Cimduo and Temixys (both of which contain lamivudine 300 mg/TDF 300 mg) and Symfi (efavirenz 600 mg/lamivudine 300 mg and TDF 300 mg) after reviewing the results of a clinical trial that compared the use of TDF to the use of stavudine when each drug was administered with lamivudine and efavirenz.[5,12] This trial showed that TDF and stavudine had similar virologic response; however, TDF had lower toxicity than stavudine.

FDA approval of Symfi Lo (efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg) was based on a study that compared the use of efavirenz 400 mg to the use of efavirenz 600 mg, each administered with emtricitabine 200 mg and TDF 300 mg, in 630 ARV-naive adults.[13] See the efavirenz section for a detailed discussion of this study.

In children, the published efficacy data for TDF are mixed, but potency equal to that in adults has been seen in pediatric patients aged 3 years to 18 years with susceptible virus. In children aged 2 years to <12 years, TDF 8 mg/kg/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 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 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 if 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) 1 and 2 may be at higher risk of decreased BMD than children with more advanced pubertal development (i.e., SMR ≥3).[21] Discontinuation of TDF results in partial or complete recovery of BMD.[25]

In the industry-sponsored study that led to FDA approval of TDF in adolescents aged ≥12 years and weighing ≥35 kg, six of 33 participants (18%) in the TDF arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks, while only one of 33 participants (3%) in the placebo arm experienced this decline.[16]

TDF administration disrupts vitamin D metabolism,[28,29] 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.[30] During chronic TDF administration, youth with HIV who received vitamin D3 supplements (50,000 IU once monthly) had decreased serum parathyroid hormone compared to study participants not treated with high doses of vitamin D3[31] and increased lumbar spine BMD.[29] 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 ART regimen that included TDF and who received vitamin D3 2,000 IU or 4,000 IU daily.[32] Since this improvement in lumbar spine BMD was seen in patients with and without

baseline vitamin D deficiency, some practitioners recommend vitamin D supplementation in all patients who are being treated with TDF-containing ART.

Plasma concentrations of the TDF metabolite plasma TFV have been associated with TDF-related endocrine disruption and low BMD.[28] Tenofovir alafenamide (TAF), which is associated with lower plasma TFV concentrations than TDF, causes less decline in BMD than TDF (see the tenofovir alafenamide section for more information). Consider switching from TDF to TAF in patients for whom loss of BMD is of 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 absorptiometry (DXA) monitoring for children or adolescents who are being treated with TDF. Given the potential for BMD loss in children treated with TDF, some experts perform a DXA before initiating TDF therapy and approximately 6 months after starting TDF, especially in prepubertal patients and those who are in the early stages of puberty (i.e., SMR 1 and 2). If DXA results are abnormal, consider referring the patient to a subspecialist in pediatric endocrinology or a related field.

Despite the ease of use of a once-daily drug and the efficacy of TDF, the potential for BMD loss during the important period of rapid bone accrual in childhood and early adolescence is concerning and favors use of abacavir or TAF in children with SMRs 1 to 3, because children with perinatally acquired HIV are at risk for low peak bone mass.[33,34]

Renal Toxicity

New onset renal impairment and worsening renal impairment have been reported in adults[35] and children[36,37] receiving TDF. In one study, renal toxicity led to discontinuation of TDF in six of 159 (3.7%) of children with HIV who were treated with TDF.[18] While TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.[35,36] Irreversible renal failure is quite rare, but cases have been reported.[38]

The main target of TDF nephrotoxicity is the renal proximal tubule.[36] Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.[39,40]

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 two of 48 children (4%) who were not treated with TDF.[41] The risks of TDF-associated proteinuria and chronic kidney disease increase with the duration of treatment.[42,43] Of 89 participants aged 2 years 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]

Plasma TFV is the TDF metabolite most closely associated with both glomerular[28,44] and proximal tubular[45] toxicity. TAF, which generates lower plasma TFV concentrations than TDF, is associated with lower risk of renal toxicity than TDF (see the tenofovir alafenamide section).

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 prior to drug initiation. 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 urine concentration of albumin, and proximal renal tubular damage increases urine concentrations of low-molecular-weight proteins like beta-2 microglobulin, dipstick urinalysis (measuring primarily 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 nonalbumin proteinuria that is seen in TDF-associated nephrotoxicity.[46,47] While 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 tubular damage.

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Zidovudine (ZDV, Retrovir) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Capsule: 100 mg

Tablet: 300 mg

Syrup: 10 mg/mL

Concentrate for Injection or Intravenous Infusion: 10 mg/mL

Generic Formulations:

- Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

Fixed-Dose Combination Tablets:

- [*Combivir and Generic*] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [*Trizivir <mark>and Generic</mark>*] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

Dosing Recommendations

Note: Zidovudine is frequently used in neonates to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12 for information about using zidovudine to prevent perinatal transmission.

Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth[a]

Gestational Age at Birth	Oral Zidovudine Dose
≥35 weeks	Birth to Age 4 Weeks: • Zidovudine 4 mg/kg orally 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 zidovudine 4 mg/kg orally twice daily from birth to age 4 weeks.

Weight Band	Volume of Zidovudine 10 mg/mL Oral Syrup Twice Daily
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:
• Zidovudine 12 mg/kg orally twice daily

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 zidovudine) and myositis

Special Instructions

- Give zidovudine without regard to food.
- If substantial granulocytopenia or anemia develops in patients receiving zidovudine, 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.
- When using fixed-dose combination (FDC) tablets that contain zidovudine, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

Metabolism/Elimination

- Zidovudine is eliminated primarily by

Gestational Age at Birth	Oral Zidovudine Dose
≥30 weeks to <35 weeks	Birth to Age 2 Weeks: • Zidovudine 2 mg/kg orally twice daily Aged 2 Weeks to 6 to 8 Weeks: • Zidovudine 3 mg/kg orally twice daily Aged >6 Weeks to 8 Weeks: • Zidovudine 12 mg/kg orally twice daily
<30 weeks	Birth to Age 4 Weeks: • Zidovudine 2 mg/kg orally twice daily Aged 4 Weeks to 8 to 10 Weeks: • Zidovudine 3 mg/kg orally twice daily Aged >8 Weeks to 10 Weeks: • Zidovudine 12 mg/kg orally 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

Zidovudine Weight-Based Dosing

Body 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:

- Zidovudine 180 mg to 240 mg per m^2 of body surface area every 12 hours

Adolescent (Aged ≥18 Years) and Adult Dose:

- Zidovudine 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

hepatic metabolism. The major metabolite is zidovudine glucuronide, which is renally excreted.

- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.

Zidovudine Dosing in Patients with Renal Impairment:

- A zidovudine dose adjustment is required in patients with renal insufficiency.

Zidovudine Dosing in Patients with Hepatic Impairment:

- The dose of zidovudine may need to be reduced in patients with hepatic impairment.

- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min or in patients who are on dialysis or who have impaired hepatic function.

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[a] For premature infants who are diagnosed with HIV infection, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

Drug Interactions (see also 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.

- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues, such as ribavirin, antagonize *in vitro* antiviral activity of zidovudine.

- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine **should be avoided**. Doxorubicin may inhibit the phosphorylation of zidovudine 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 and zidovudine than in infants who are receiving only zidovudine.[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:* There is a possible increased risk of cardiomyopathy.[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.

Pediatric Use

Approval

Zidovudine 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 and lamivudine.[3-19] Pediatric experience with zidovudine both for treating HIV and for preventing perinatal transmission is extensive. However, the mitochondrial toxicity of zidovudine leads many experts to favor the use of abacavir 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 zidovudine and lamivudine has been extensively studied in children and has been a part of ART regimens in many trials. The safety and efficacy of zidovudine plus lamivudine were compared to the safety and efficacy of abacavir plus lamivudine and stavudine plus lamivudine in children aged <5 years in the CHAPAS-3 study. All regimens also included either nevirapine or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.[20] Pediatric patients who received zidovudine plus abacavir or zidovudine plus lamivudine had lower rates of viral suppression and experienced more adverse events that required regimen modification than patients who received abacavir/lamivudine.[21,22]

Infants with Perinatal HIV Exposure

The PACTG 076 clinical trial demonstrated that administering zidovudine to pregnant women and their infants could reduce the risk of perinatal transmission by nearly 70%.[23] See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) for further discussion of the use of zidovudine for the prevention of perinatal transmission of HIV. A dose of approximately zidovudine 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 zidovudine (see Pharmacokinetics below). The rate-limiting step in the phosphorylation of zidovudine to active zidovudine triphosphate is the limited amount of thymidylate kinase. Increasing doses of zidovudine will lead to increased zidovudine plasma concentrations and increased intracellular concentrations of zidovudine monophosphate but not zidovudine diphosphate or zidovudine triphosphate.

In 31 infants who received zidovudine to prevent perinatal transmission, levels of intracellular zidovudine metabolites were measured after delivery. Plasma zidovudine and intracellular zidovudine monophosphate decreased by roughly 50% between post-delivery Day 1 and Day 28, whereas zidovudine diphosphate and zidovudine triphosphate remained low throughout the sampling period.[24] Zidovudine dose is poorly correlated with the active form of zidovudine 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). This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during zidovudine use in the first 4 weeks of life and will make it easier for caregivers to administer zidovudine oral syrup to their infants. The changes in weight and the small differences in zidovudine dose will have minor effects on the intracellular concentrations of zidovudine triphosphate.

Infants with HIV Infection

For full-term neonates who are diagnosed with HIV infection during the first days to weeks of life, the zidovudine dose should be increased at age 4 weeks to the continuation dose (see the dosing table). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically during the first 4 weeks to 6 weeks of life in full-term neonates. This increase in metabolizing enzyme activity leads to an increased clearance of plasma zidovudine, and the dose of zidovudine should be adjusted when zidovudine is used to treat HIV after the first 4 weeks in full-term infants.

For premature infants who are diagnosed with HIV infection, the time to increase the zidovudine 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 zidovudine PK in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends the following: in infants with HIV who were born at ≥30 weeks to <35 week switch to a dose of zidovudine 12 mg/kg twice daily at a post-gestational age of 6 weeks to 8 weeks; for infants who are born at <30 weeks, switch to zidovudine 12 mg/kg twice daily at a post-gestational age of 8 weeks to 10 weeks.[25] Careful clinical assessment of the infant, evaluation of hepatic and renal function, and review of concomitant medications should be performed prior to increasing the zidovudine dose to that recommended for full-term infants.

Pharmacokinetics

Zidovudine undergoes intracellular metabolism to achieve its active form, zidovudine triphosphate. Phosphorylation requires multiple steps: zidovudine is phosphorylated by thymidine kinase to zidovudine monophosphate; zidovudine monophosphate is phosphorylated by thymidylate kinase to zidovudine diphosphate; and zidovudine diphosphate is phosphorylated by nucleoside diphosphate kinase to zidovudine triphosphate. Overall, zidovudine PKs in pediatric patients aged >3 months are similar to those seen in adults. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing **is not recommended** because of the low intracellular zidovudine triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.[26] PK studies such as PACTG 331 demonstrate that dose adjustments are necessary for premature infants, because they have reduced clearance of zidovudine compared with the

clearance observed in term newborns of similar postnatal ages.[4] Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease.[15]

Toxicity

Several studies suggest that the adverse hematologic effects of zidovudine may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean plasma area under the curve values for zidovudine.[3,4,27]

Incidence of hematological toxicity was investigated in the ARROW study, which randomized treatment-naive Ugandan/Zimbabwean children to receive either zidovudine-containing regimens or abacavir-containing regimens. The incidence of severe anemia was similar regardless of zidovudine use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. Zidovudine use was associated with severe neutropenia in a small number of children.[28]

Zidovudine is associated with greater mitochondrial toxicity than abacavir and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than stavudine.[29,30]

While 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 zidovudine may increase the risk.[2] Recent analysis of data from a U.S.-based, multicenter, prospective cohort study (PACTG 219/219C) found that ongoing zidovudine exposure was independently associated with a higher rate of cardiomyopathy.[2]

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Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

Doravirine (DOR, Pifeltro)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence, TMC 125)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant, TMC 278)

Doravirine (DOR, Pifeltro) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Tablet: 100 mg

Fixed-Dose Combination Tablet:

- [*Delstrigo*] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg

Dosing Recommendations

Child and Adolescent Dose:

- Doravirine is not approved for use in children or adolescents aged <18 years.

Adult (Aged ≥18 Years) Dose

Antiretroviral-Naive Patients:

- Doravirine 100 mg once daily

[*Delstrigo*] Doravirine/Lamivudine/TDF

Adult (Aged ≥18 Years) Dose:

- One tablet once daily

Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

Special Instructions

- Doravirine can be taken with or without food.
- Do not use doravirine with other non-nucleoside reverse transcriptase inhibitors.
- When doravirine is coadministered with rifabutin, the dose of doravirine should be increased to 100 mg twice daily. When doravirine/lamivudine/TDF (Delstrigo) is coadministered with rifabutin, an additional dose of freestanding doravirine (Pifeltro) needs to be administered approximately 12 hours later.
- Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains lamivudine and TDF. Severe acute exacerbation of HBV can occur when lamivudine or TDF is discontinued; therefore, hepatic function should be monitored for several months after halting therapy with lamivudine or TDF.
- See the lamivudine and TDF sections of the Drug Appendix for special instructions and additional information about the individual drug components of Delstrigo.

Metabolism/Elimination

- Doravirine is metabolized by the enzyme cytochrome P450 3A.

- Doravirine has multiple interactions with several drugs (see text below).

Doravirine Dosing in Patients with Hepatic Impairment:

- Dose adjustment is not required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in patients with severe hepatic impairment.

Doravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required when using doravirine in patients with mild, moderate, or severe renal impairment. Doravirine use has not been studied in patients with end-stage renal disease nor in patients on dialysis.

- Doravirine administered with lamivudine and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- Doravirine 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 doravirine plasma concentrations and potential decreases in efficacy and may lead to the development of resistance. Before doravirine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with doravirine.

- Doravirine **should not be coadministered** with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz, etravirine, and nevirapine.[1,2]

- Doravirine **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.[1,2]

- Drug interactions between doravirine and rifabutin induce the metabolism of doravirine and require an additional doravirine 100 mg to be administered as a separate dose 12 hours apart.[1-3]

Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams.
- *Less common (more severe):* Neuropsychiatric adverse events, including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

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. Doravirine is expected to have activity against HIV with isolated NNRTI resistance that is associated with substitutions

at positions 103, 181, or 190. However, some single mutations and combinations of the viral mutations have been shown to significantly decrease the susceptibility to doravirine. Specifically, clinical HIV isolates containing the Y188L substitution alone or in combinations with K103N or V106I; combination of V106A with G190A and F227L; or combination of E138K with Y181C and M230L, have shown ≥100-fold reduction in susceptibility to doravirine.[1,2] In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of doravirine.

Pediatric Use

Approval

Doravirine is not approved by the Food and Drug Administration for use in children or adolescents aged <18 years.

Efficacy in Clinical Trials

The efficacy of doravirine was evaluated using 48 weeks of data from two randomized, multicenter, double-blind, active controlled Phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD) that enrolled participants with HIV who had no history of antiretroviral treatment (N = 1,494).[4,5]

In DRIVE-FORWARD, adult subjects received either doravirine 100 mg (N = 383) or darunavir 800 mg plus ritonavir 100 mg (N = 383) once daily, each in combination with emtricitabine/tenofovir disoproxil fumarate (TDF) or abacavir/lamivudine. Eighty-four percent of patients who received doravirine and 80% of patients who received darunavir and ritonavir had HIV RNA <50 copies/mL at Week 48.[4]

In DRIVE-AHEAD, adult subjects received either coformulated doravirine/lamivudine/TDF (N = 364) or efavirenz/emtricitabine/TDF once daily (N = 364). Similar to DRIVE-FORWARD, 84% of participants who received doravirine/lamivudine/TDF and 81% of participants who received efavirenz/emtricitabine/TDF achieved virologic suppression (HIV RNA <50 copies/mL) at Week 48 of the DRIVE-AHEAD trial.[5]

Pharmacokinetics

The pharmacokinetics of doravirine have been evaluated in treatment-naive adults aged ≥18 years. A Phase 2 trial evaluated doravirine over a dose range of 0.25 times to 2 times the recommended dose of doravirine in treatment-naive participants with HIV who also received emtricitabine/TDF. No exposure-response relationship for efficacy was reported for doravirine.[5]

Toxicity

In the DRIVE-AHEAD clinical trial, 24% of participants who received coformulated doravirine/lamivudine/TDF and 57% of participants who received efavirenz/emtricitabine/TDF reported one or more neuropsychiatric adverse events.[5] Mild to moderate in severity adverse events were reported in 97% among the participants who received doravirine/lamivudine/TDF and in 96% of those who received efavirenz/emtricitabine/TDF. The majority of participants reported these events during the first 4 weeks of treatment in both groups. Neuropsychiatric adverse events led to treatment discontinuation for 1% of participants in both groups. At Week 48, the prevalence of neuropsychiatric adverse events was 12% in the doravirine/lamivudine/TDF group and 22% in the efavirenz/emtricitabine/TDF group.[5]

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Efavirenz (EFV, Sustiva) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Capsules: 50 mg, 200 mg
Tablet: 600 mg
Generic Formulations:
- 50 mg capsules
- 200 mg capsules
- 600 mg tablets

Fixed-Dose Combination Tablets:
- [*Atripla and Generic*] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- <mark>[*Symfi*] Efavirenz 600 mg/lamivudine 300 mg/TDF 300 mg</mark>
- [*Symfi Lo*] Efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg

Dosing Recommendations

Neonatal Dose:
- Efavirenz is not approved for use in neonates.

Pediatric Dose
- Efavirenz 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 efavirenz in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.
- **Note:** If the use of efavirenz is unavoidable due to a clinical situation, the Panel suggests using investigational doses of efavirenz in this age group (see investigational dosing Table A in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below). Evaluation of cytochrome P450 (CYP) 2B6 genotype is required prior to use in this age group. Therapeutic drug monitoring (TDM) should be used and efavirenz plasma concentration should be measured 2 weeks after initiation. If a child initiated efavirenz at an investigational dose while <3 years of age, some experts would also measure plasma

Selected Adverse Events
- Rash, which is generally mild and transient and appears to be more common in children than in adults
- Central nervous system (CNS) symptoms such as fatigue, poor sleeping patterns, insomnia, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation
- Use of efavirenz may produce false-positive results with some cannabinoid and benzodiazepine tests
- Gynecomastia
- Hepatotoxicity
- Corrected QT prolongation

Special Instructions
- Efavirenz can be swallowed as a whole capsule/tablet or 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.
- Administer efavirenz, Atripla, <mark>Symfi</mark>, or Symfi Lo on an empty stomach. Avoid administration with a high-fat meal, because this has the potential to increase absorption.
- When using fixed-dose combination (FDC) tablets, see other drug sections in the

concentration at age 3 years after the child transitions to the recommended dose for children aged ≥3 years (see the Therapeutic Drug Monitoring section in the text below). When making a dose adjustment based on efavirenz concentrations, consultation with an expert in pediatric HIV infection is recommended.

Children Aged ≥3 Years and Weighing ≥10 kg:
Once-Daily Doses of Efavirenz by Weight

Weight	Efavirenz 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).

[b] Some experts recommend a dose of efavirenz 367 mg/m^2 body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see Pediatric Use in text below for details). Weight bands approximate a dose of efavirenz 367 mg/m^2, with a maximum dose of 600 mg.

Child and Adolescent (Weighing ≥40 kg) and Adult Dose:
- Efavirenz 600 mg once daily

[*Atripla*] Efavirenz 600 mg/Emtricitabine/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

Drug Appendix for special instructions and additional information about the individual drug components.
- The Food and Drug Administration cautions that efavirenz 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 efavirenz in female adolescents and adults who are pregnant or may become pregnant.

Instructions for Use of Efavirenz Capsule as a Sprinkle Preparation with Food or Formula:
- Hold capsule horizontally over a small container and carefully twist to 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

- CYP2B6 is the primary enzyme for efavirenz metabolism.
- Cytochrome P450 (CYP) 3A and CYP2B6 inducer *in vivo* and CYP2C9, 2C19, and 3A4 isozyme inhibitor *in vitro*.
- Efavirenz **is not recommended** for patients with moderate or severe hepatic impairment.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450, with slower metabolizers at higher risk of toxicity (see Therapeutic Drug Monitoring in the text below for information about the management of mild or moderate toxicity).

Atripla, Symfi, and Symfi Lo Dosing in Adults with Renal Impairment:
- Because these are FDC products and TDF, lamivudine, and emtricitabine require dose adjustments based on renal function, Atripla, Symfi, and Symfi Lo should not be used in patients with creatinine clearance <50 mL/min or in patients on dialysis.

Note: Symfi Lo has not been studied in children (sexual maturity rating [SMR] 1–3), and major inter-individual variability in efavirenz plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400 mg dose of efavirenz may be too low in children or adolescents with SMRs 1 to 3 who weigh ≥40 kg. TDM is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh ≥40 kg.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Metabolism:* Coadministration of efavirenz with drugs 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 efavirenz, resulting in lower plasma concentrations. There is potential for multiple drug interactions with efavirenz. Importantly, dose adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, lopinavir/ritonavir (LPV/r), or maraviroc.

- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

- Corrected QT (QTc) prolongation has been observed with the use of efavirenz.[1,2] Consider using an alternative to efavirenz 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.

- *Rare:* QTc prolongation has been observed with the use of efavirenz.[1,2] A case report associated efavirenz use with marked QT prolongation and Torsades de Pointes.[3] An association between efavirenz 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.

- *Potential risk of teratogenicity:* See Efavirenz in the Perinatal Guidelines.

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

Efavirenz has been approved by the 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 efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing ≥35 kg.

Efficacy in Clinical Trials

Efavirenz-based regimens have proven virologically superior or noninferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.[4-10] Efavirenz proved inferior to dolutegravir in the SINGLE trial in adults, which compared the virologic response of dolutegravir plus abacavir/lamivudine to the virologic response of efavirenz/TDF/emtricitabine at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.[11]

In clinical trials in adults and children with HIV, efavirenz used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. FDA approval of Symfi (efavirenz 600 mg/lamivudine/TDF) was based on the results from a clinical trial that compared the use of TDF to the use of stavudine when each drug was administered with lamivudine and efavirenz.[12] This trial showed that these regimens were similarly effective. The 96-week results of the Encore1 trial, a randomized trial in adults, showed that efavirenz 400 mg used in combination with TDF and emtricitabine was noninferior to efavirenz 600 mg used in combination with TDF and emtricitabine.[13] Efavirenz used in combination with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety that is comparable to what has been seen in adults.[14-20]

FDA approval of Symfi Lo (efavirenz 400 mg/lamivudine 300 mg/TDF 300 mg) was based on a comparison between efavirenz 400 mg and efavirenz 600 mg, both taken with emtricitabine 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 Caucasian. This study showed similar rates of viral load suppression and toxicities among participants in each group.[13] Since efavirenz clearance is related to age and to CYP2B6 polymorphisms, and since allele frequency varies by ethnicity, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommend caution when using the lower-dose efavirenz formulation in pediatric patients weighing ≥40 kg and suggest the use of therapeutic drug monitoring (TDM) in these patients.

Pharmacokinetics: Pharmacogenomics

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of efavirenz may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for efavirenz metabolism, and pediatric patients with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher efavirenz levels in these patients than in those with the G/G or G/T genotypes.[21-25] 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.[26] A retrospective study confirmed the inter-individual variability of efavirenz plasma concentration among pediatric patients in a multi-ethnic, high-income setting, and the differences could be explained in large part by polymorphisms in drug metabolizing genes as well as by age at treatment initiation and time from treatment initiation.[27] IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/kg of efavirenz using opened capsules resulted in therapeutic efavirenz 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.[28] Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see discussion below).[25,28] Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.[25,29-33] The CYP2B6 T983C mutation has also been associated with reduced efavirenz clearance in African children.[25]

Pharmacokinetics and Dosing: Infants and Children Aged <3 Years

The Panel **does not recommend** the use of efavirenz 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.[23,34] These data show age-related differences in absorption and impact of formulation on efavirenz PKs.[24] Also, hepatic enzyme activity is known to change with age. Using a pharmacometric model, the increase in oral clearance of efavirenz as a function of age is predicted to reach 90% of mature value by age 9 months.[24] This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.[24] 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 genotypes.[21] In children with the CYP2B6-516-G/G genotype, the oral clearance rate of efavirenz has been shown to be higher in children aged <5 years than in older children.[21] 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 HIV/tuberculosis coinfection, using doses of efavirenz 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]; 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 efavirenz 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 efavirenz.[28] 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.

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 (Extensive Metabolizers)[a]	Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (Slow Metabolizers)[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 IMPAACT study P1070.[28] Evaluation of CYP2B6 genotype is required. Therapeutic drug level monitoring is recommended, with a trough measured 2 weeks after initiation of efavirenz and again at age 3 years for a possible dose adjustment.

The FDA-approved doses of efavirenz 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 PACTG 1021 and PACTG 382, and also from data collected during AI266-922, a study that assessed the PKs, safety, and efficacy of 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. There is concern that FDA-approved doses may result in frequent underdosing in CYP2B6 EMs. PK modeling, based on P1070 PK data, was used to generate estimates of the percentage of participants who were likely to reach therapeutic efavirenz target concentrations on FDA-indicated dosages,

according to the participants' genotypes.[28] The frequency of area under the curve (AUC) in the target range of 35 to 180 mcg*h/mL and C_{24h} in the target range of 1 mg/L to 4 mg/L, a systemic exposure similar to that shown to be safe and effective in older children and adults, was calculated.[28] The P1070 genotype-based dosing resulted in approximately 80% of EM participants and 90% of SM participants achieving the targeted AUC, whereas the FDA-approved dosing would result in an estimated 63% of EM participants and 44% of SM participants achieving the target AUC. In addition, using FDA-approved dosing would result in an estimated one-third of EM children with subtherapeutic efavirenz exposures and more than half of SM children with AUCs above the target range.

The Panel **does not recommend** use of efavirenz in children aged 3 months to <3 years. If the clinical situation demands the use of efavirenz, 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, measuring efavirenz plasma concentrations should be considered 2 weeks after initiation (see the Therapeutic Drug Monitoring section below). The mid-dose efavirenz plasma concentration target of 1.0 to 4.0 mg/L derived from adult clinical monitoring data is typically also applied to trough concentrations. A study of 128 African children (aged 1.7–13.5 years) suggests that the C_{24h} threshold for increased risk of unsuppressed viral load is C_{24h} 0.65 mg/L.[35] Consultation with an expert in pediatric HIV infection is recommended before adjusting dose. In addition, when following the P1070 investigational dose recommendations, some experts would measure efavirenz 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, efavirenz concentrations can be suboptimal.[21,36-40] Therefore, some experts recommend TDM with efavirenz and possible use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In one study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered dose was efavirenz 13 mg/kg (367 mg/m^2) and the range was from 3 mg/kg to 23 mg/kg (69 mg/m^2–559 mg/m^2).[41] A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/m^2 and 75 mg/m^2 twice daily plus efavirenz 350 mg/m^2 once daily showed that lopinavir trough values were adequate but suggested that the efavirenz trough values were lower than PK targets. The authors therefore concluded that higher doses of efavirenz might be needed when these drugs are used together.[42]

Toxicity: Children versus Adults

The toxicity profile for efavirenz 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.[43] 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. In adults, CNS symptoms are commonly reported, affecting 29.6% of patients in one meta-analysis of randomized trials.[44] These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. For patients who can swallow capsules or tablets, ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. The ENCORE1 study in adults demonstrated that a dose of efavirenz 400 mg is associated with fewer AEs and a noninferior virologic response when compared with the recommended 600-mg dose of efavirenz in adults.[13,45]

An association between efavirenz 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 START Trial, a prospective analysis of adults.[46,47] This association, however, was not found in analyses of two large observational cohorts,[48,49] and no cases of suicide were

reported in a systematic review of randomized trials.[44] In several studies, the incidence of neuropsychiatric AEs was correlated with efavirenz plasma concentrations, and the symptoms occurred more frequently in patients with higher concentrations.[50-54] In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously. Adverse CNS events occurred in 14% of children who received efavirenz in clinical studies[55] and in 30% of children with efavirenz concentrations >4 mg/L.[22] CNS AEs may be harder to detect in children because it is difficult to assess neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients.

Toxicity: QTc Prolongation

CYP2B6 genetic variants are known to slow efavirenz clearance. The CYP2B6*6 allele is associated with reduced clearance and increased efavirenz-induced CNS toxicity, hepatic injury, and treatment discontinuation.[50,51] Homozygous carriers of the CYP2B6*6 allele (CYP2B6*6/*6) may be at increased risk for efavirenz-induced QTc prolongation. The CYP2B6*6 allele codes for the CYP2B6-516-G>T complementary DNA nucleotide change;[56] therefore, CYP2B6*6/*6 carriers can be categorized as SMs. The effect of efavirenz on the QTc interval was evaluated in a study of 58 healthy adult subjects that collectively represented a variety of 58 healthy adult subjects, with a mix of CYP2B6 polymorphisms represented within the group. A positive relationship between efavirenz concentration and QTc prolongation was observed. The mean QTc prolongation and its upper-bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6*6/*6 genotype following the administration of efavirenz 600 mg daily for 14 days.[1] Drugs that prolong the mean QTc interval by more than 20 ms have a substantially increased likelihood of being pro-arrhythmic. While the data on drugs that prolong the mean QTc interval by more than 5 ms but less than 20 ms are inconclusive, some of these drugs have been associated with pro-arrhythmic risk.[57] Consider using an alternative to efavirenz 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 of Torsades de Pointes.[2]

Therapeutic Drug Monitoring

In the setting of potential toxicity, it is reasonable for a clinician to use TDM to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.[58,59] Dose reduction would be considered appropriate management of drug toxicity; however, dose reduction should be used with caution. Also, TDM should be considered when dosing efavirenz in 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 efavirenz, such as the dose found in Symfi Lo, in children weighing ≥40 kg. Two weeks after the initiation of efavirenz in patients aged <3 years, clinicians should measure the plasma concentration of efavirenz. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting dosage. If a child initiated efavirenz at an investigational dose while <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 efavirenz 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.[51] A recent study in children showed that a higher proportion of children with a C_{12h} <1 mg/L showed evidence of viral replication than those with a C_{12h} >1 mg/L.[60] However, the validity using a single target has been called into question.[61] In addition, a lower limit of C_{12h} > 0.7mg/L was most predictive of virologic outcome in a study of 180 adults.[62] 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.[35]

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Etravirine (ETR, Intelence) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 25 mg, 100 mg, 200 mg

Dosing Recommendations

Neonate/Infant Dose:
- Etravirine is not approved for use in neonates/infants.

Child Dose:
- Etravirine is not approved for use in children aged <2 years. Studies in infants and children aged 2 months to 2 years are under way.

Etravirine Dosing Table for Antiretroviral-Experienced Children and Adolescents <mark>Aged 2 Years to 18 Years and Weighing ≥10 kg</mark>

Body Weight	Dose
<mark>10 kg</mark> to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
≥30 kg	200 mg twice daily

Adult Dose for Antiretroviral-Experienced Patients:
- 200 mg twice daily with food

Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

Special Instructions

- Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. Always administer etravirine with food. The type of food does not affect the exposure to etravirine.

Instructions for Dispersing Etravirine Tablets in Liquid:
- Patients who are unable to swallow etravirine tablets may disperse the tablets in liquid.
- Place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication, and stir well until the water looks milky. <mark>Add approximately 15 mL (1 tablespoon) of additional liquid. Water may be used, but other liquids, such as orange juice or milk, may improve the taste of the medication.</mark> Patients should not place the tablets in orange juice or milk without first adding water. <mark>Warm beverages (with temperatures >104°F or >40°C) or carbonated beverages should be avoided.</mark>
- Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.
- Etravirine tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.

Metabolism/Elimination

- Etravirine 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.
- Etravirine is involved in multiple interactions with antiretroviral agents and other drugs (see text below).

Etravirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is required when using etravirine 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 for patients with renal impairment.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- Etravirine is associated with multiple drug interactions. A patient's medication profile should be carefully reviewed for potential drug interactions before etravirine is administered.

- Etravirine **should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs).

- Etravirine **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine, efavirenz, rilpivirine, doravirine).

- Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir,[1] but no dose adjustment is currently recommended when etravirine and raltegravir are used together. Etravirine significantly reduces plasma concentrations of dolutegravir, elvitegravir/cobicistat (EVG/COBI), and darunavir/cobicistat.[2] Dolutegravir should only be used with etravirine when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir (DRV/r), or lopinavir/ritonavir. Etravirine **should not be coadministered** with EVG/COBI.

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 etravirine. However, patients who have a history of severe rash with prior NNRTI use **should not receive etravirine**.

- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme have all been reported. Instances of severe rash have included Stevens-Johnson syndrome, and HSRs have included constitutional findings and organ dysfunction, including hepatic failure. Discontinue etravirine 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 etravirine after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using nevirapine or efavirenz **should not receive etravirine**.

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

Etravirine is approved by the Food and Drug Administration for use in antiretroviral (ARV)-experienced children and adolescents aged 2 years to 18 years.

Efficacy in Clinical Trials

In the PIANO study,[3] ARV-experienced children aged 6 years to <18 years received etravirine with a ritonavir-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/mm³ from baseline. At Week 48, 68% of children aged 6 years to <12 years had plasma HIV RNA <50 copies/mL, while 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 etravirine-based therapy, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.[4]

Pharmacokinetics

In a Phase 1 dose-finding study that involved children aged 6 years to 17 years, 17 children were given etravirine 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.[5] However, a higher dose (etravirine 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 etravirine concentrations in the lowest quartile (<2,704 ng*h/mL or 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 etravirine concentrations in the upper three quartiles.[6]

Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily

	Mean Etravirine AUC_{0-12h} (ng*h/mL)	Mean Etravirine C_{0h} (ng/mL)
Children Aged 6 Years–11 Years (N = 41)	5,684	377
Adolescents Aged 12 Years–17 Years (N = 60)	4,895	325
Adults (N = 575)	5,506	393

Key to Acronyms: AUC_{0-12h} = area under the curve for 12 hours post-dose; C_{0h} = pre-dose concentration during chronic administration

IMPAACT P1090 examined the PKs and safety of etravirine in treatment-experienced children with HIV aged ≥2 years to <6 years.[7] Etravirine 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 etravirine AUC_{0-12h} values fell below the target range of 60% of the values seen in adults. Subsequent participants were given doses of twice-daily etravirine that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg per dose and children weighing 20 kg to <25 kg were given 125 mg per dose.

The tablets were swallowed whole or dispersed in liquid. The protocol-specified PK targets for etravirine were achieved at these doses; the geometric mean AUC_{0-12h} was 3,504 ng*hr/mL, which was within the target range of 2,713 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 five of 14 participants (36%) having AUC_{0-12h} values that were below the tenth percentile for the adult AUC_{0-12h} range (<2,350 ng*hr/mL).The etravirine AUC_{0-12h} values were significantly lower in children who received dispersed tablets than in children who swallowed intact etravirine tablets: 2,841 ng*hr/mL versus 10,721 ng*hr/mL, respectively ($P < 0.0001$).

Five children with HIV aged 1 year to <2 years were also enrolled in P1090. The etravirine exposure in these children was lower than the etravirine exposure reported in adults; the AUC_{0-12h} geometric mean ratio was 0.59 (90% confidence interval, 0.34–1.01). Virologic failure, which was defined as a confirmed viral load ≥400 copies/mL, occurred in three of four evaluable children by Week 24.

Etravirine is often combined with DRV/r for treatment of adults with HIV who have previously experienced virologic failure. Cressey et al. examined PK data from 36 adolescents and young adults receiving etravirine 200 mg twice daily in combination with DRV/r 600 mg/100 mg twice daily. The PK exposures of both agents were similar to those seen in adults, although interindividual variability was high.[8] The PKs of etravirine and darunavir were also studied in adolescents and young adults receiving DRV/r 800 mg/100 mg once daily with either etravirine 200 mg twice daily or etravirine 400 mg once daily.[9] Darunavir concentrations were higher when darunavir was coadministered with etravirine, particularly when the latter was given in doses of 200 mg twice daily. Etravirine exposures were lower when etravirine was given with DRV/r, particularly when etravirine was given twice daily; however, the authors noted that these studies had limited sample sizes. While the combination of etravirine and DRV/r was effective in a small cohort of adolescents with HIV[10] and in 51% of participants in the PIANO study,[3,6] these data suggest a need for additional data on the PK interactions for etravirine and other ARV agents in pediatric patients. Most notably, data is needed on regimens that do not include ritonavir-boosted PIs. Until such data become available, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends using etravirine as part of a regimen that includes a ritonavir-boosted PI.

P1090 evaluated the antiviral activity of etravirine in treatment-experienced pediatric patients with HIV aged ≥2 years to <6 years. At baseline, the mean plasma HIV RNA viral load was approximately 247,000 copies/mL, the median CD4 cell count was 818 cells/mm³, and the mean CD4 percentage was 26%. At Week 24, etravirine administered in combination with other ARV drugs produced a virologic response (defined as HIV RNA <400 copies/mL) in 15 of 16 evaluable participants (94%). The median CD4 cell count increase from baseline to Week 24 was 298 cells/mm³, and the median CD4 percentage increase was 5%.

Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions deemed possibly related to etravirine. 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%). In 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. Ten participants (50%) developed rashes within 4 weeks of beginning the study, but these rashes were not attributed to the use of etravirine. In this study, rash occurred in 6% of female patients and 7% of male patients, and no subjects discontinued the study prematurely due to rash. Diarrhea occurred in five of 20 patients (25%).

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Nevirapine (NVP, Viramune) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: Immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg
Suspension: 10 mg/mL

Generic Formulations:

- Immediate-release 200 mg tablets
- Extended-release (XR) 400 mg tablets

Note: While the suspension formulation of brand-name nevirapine (Viramune) is available, it is not typically stocked in local pharmacies or hospitals. Have the pharmacy ask their drug wholesaler to order from the Boehringer-Ingleheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

Dosing Recommendations

Note: Nevirapine is often used to prevent perinatal transmission of HIV. See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV for information about nevirapine dosing in neonates aged ≤1 days.

Child and Adolescent Dose:

- **Note:** In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years.[a]

Immediate-Release Tablets and Suspension Formulations

Gestational Age 34 Weeks–37 Weeks:

- Nevirapine 4 mg/kg per dose twice daily for the first week, increasing to nevirapine 6 mg/kg per dose twice daily thereafter (no lead-in dosing).[a]
- This is an **investigational dose** that is not approved by the Food and Drug Administration (FDA).

Gestational Age ≥37 Weeks to Age <1 Month:

- Nevirapine 6 mg/kg per dose twice daily (no lead-in dosing).[a]
- This is an **investigational dose** that is not approved by the FDA.
- See the Special Considerations for Dosing: Neonates and Premature Infants section below.

Aged ≥1 Month to <8 Years:

- Nevirapine 200 mg/m^2 of body surface area per dose twice daily after lead-in dosing.[a] In children aged ≤2 years, some experts initiate

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

- Shake suspension well before administering and store at room temperature.
- Nevirapine can be given without regard to food.
- Nevirapine-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 dose until rash resolves (see Major Toxicities below).
- Nevirapine extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for >14 days, nevirapine should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement below).
- Most cases of nevirapine-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see Major Toxicities below).

nevirapine without lead-in dosing (maximum dose of immediate-release tablets is 200 mg twice daily).

Aged ≥8 Years:

- Nevirapine 120–150 mg per m^2 of body surface area per dose twice daily after lead-in dosing[a] (maximum dose of immediate-release tablets is nevirapine 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-m^2 dose as the child grows, as long as there are no adverse effects.

Extended-Release Tablets

Aged ≥6 Years:

- Patients aged ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing.[a]

Body Surface Area Dosing for Nevirapine Extended-Release Tablets

Body Surface Area Range	Nevirapine Extended-Release Tablets
0.58 m^2 to 0.83 m^2	200 mg once daily (two 100-mg tablets)
0.84 m^2 to 1.16 m^2	300 mg once daily (three 100-mg tablets)
≥1.17 m^2	400 mg once daily (one 400-mg tablet)

Adolescent and Adult Dose:

- Nevirapine 200 mg twice daily or 400 mg extended release once daily after lead-in dosing.[a,b]

Nevirapine Used in Combination with Lopinavir/Ritonavir:

- A higher dose of lopinavir/ritonavir may be needed (see the Lopinavir/ritonavir section).

Metabolism/Elimination

- Nevirapine is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a nevirapine dose is eliminated in urine as UGT-derived glucuronidated metabolites.

Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:

- An additional dose of nevirapine should be given following each dialysis session.

Nevirapine Dosing in Patients with Hepatic Impairment:

- Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

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[a] Nevirapine is usually initiated at a lower dose that is increased in a stepwise fashion. Nevirapine induces CYP metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the immediate-release formulation once daily instead of twice daily for the first 14 days of therapy. If there are no rash or other adverse effects after 14 days of therapy, increase the dose of nevirapine to the age-appropriate full dose of the immediate-release formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged ≥1 month to <8 years is nevirapine 200 mg per m^2 of body surface area once daily for the first 14 days, followed by nevirapine 200 mg per m^2 of body surface area twice daily thereafter. However, in children aged ≤2 years, some experts initiate nevirapine without lead-in dosing (see Dosing Considerations: Lead-In Requirement and Special Considerations for Dosing: Neonates and Premature Infants below). In patients who are already receiving the full twice-daily dose of immediate-release nevirapine, extended-release tablets can be used without the lead-in period. Patients must swallow nevirapine extended-release tablets whole. They must not be chewed, crushed, or divided. **Patients must never take more than one form of nevirapine at the same time.** The dose should not exceed 400 mg daily.

[b] Symptomatic hepatitis, including fatal hepatic necrosis, occurs at a significantly higher frequency in antiretroviral (ARV)-naive women with pre-nevirapine CD4 T lymphocyte (CD4) cell counts >250 cells/mm^3 and in ARV-naive men with pre-nevirapine CD4 counts >400 cells/mm^3. Nevirapine **should not be initiated** in these patients unless the benefit clearly outweighs the risk.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and [HIV Drug Interaction Checker](#))

- *Metabolism:* Nevirapine induces hepatic cytochrome P450 (CYP), including 3A and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, leading to a 1.5- to two-fold increase in nevirapine clearance. There is potential for multiple drug interactions with nevirapine. Some genetic polymorphisms of CYP2B6 are associated with increased nevirapine serum concentrations. CYP2B6 polymorphisms vary among populations and may contribute to differences in nevirapine exposure. Please see the [Efavirenz section](#) for more information on how polymorphisms can alter enzyme activity.

- Nevirapine should not be coadministered to patients who are receiving atazanavir (with or without ritonavir), because nevirapine substantially decreases atazanavir exposure.

- Nevirapine increases the metabolism of lopinavir. A dose adjustment of lopinavir is recommended when the two drugs are coadministered (see the [Lopinavir/ritonavir](#) section).

- Before nevirapine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

Major Toxicities

Note: These toxicities are seen with continuous dosing regimens, not during single-dose nevirapine 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 abnormal hepatic transaminases. Nevirapine 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. Nevirapine-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 nevirapine 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). The majority of cases occur during the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-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 cell count >250 cells/mm^3 in adult females and >400 cells/mm^3 in adult males). In children, there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with CD4 percentages >15%.[1] Hypersensitivity reactions 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. Nevirapine **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

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

Nevirapine is approved by the Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of therapy, especially in resource-limited settings.[2-10]

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 nevirapine in young children but not in older children. IMPAACT P1060 demonstrated the superiority of LPV/r over nevirapine in children aged <3 years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics enrolled older children receiving nevirapine or efavirenz and showed no differences between a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and protease inhibitor (PI)-based regimen.[11-17]

In infants and children who were previously exposed to a single dose of nevirapine to prevent perinatal transmission of HIV, nevirapine-based antiretroviral therapy (ART) is less likely to control viral load than LPV/r-based ART. In P1060, 153 children with HIV and previous exposure to nevirapine for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine and lamivudine plus either nevirapine or LPV/r. At 24 weeks post-randomization, 24% of children in the nevirapine arm had experienced virologic failure, defined as <1 $\log_{10}$ decrease in HIV RNA during Weeks 12 to 24 or HIV RNA >400 copies/mL at Week 24, compared to 7% of children in the LPV/r arm ($P = 0.0009$). When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the nevirapine arm met a primary endpoint compared to 22% of children in the LPV/r arm ($P = 0.027$).[14] Similar results were reported in a comparison study of nevirapine and LPV/r in children aged 6 to 36 months who had not been previously exposed to nevirapine. This finding suggests that LPV/r-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[11]

Extended-release nevirapine 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 nevirapine 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). Following an 11-week period with immediate-release nevirapine, participants were treated with nevirapine extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PKs) were determined.[18] 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 nevirapine extended release 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 nevirapine extended release, all 39 participants continued to have plasma HIV RNA <50 copies/mL.[19]

General Dosing Considerations

Body surface area has traditionally been used to guide nevirapine dosing in infants and young children. It is important to avoid underdosing nevirapine, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (those aged ≤8 years) have higher apparent oral clearance than older children. In order to achieve drug exposures that are equivalent to those seen in children aged >8 years, younger children require higher doses of nevirapine than older children.[7,8] Because of this, it is recommended that children aged <8 years receive nevirapine 200 mg per m² of body surface area per dose twice daily (the maximum dose of the immediate-release preparation is 200 mg twice daily) or nevirapine 400 mg per m² of body surface area administered once daily as the extended-release preparation (the maximum dose of the extended-release preparation is nevirapine 400 mg once daily). For children aged ≥8 years, the recommended dose of the immediate-release preparation is nevirapine 120 mg per m² of body surface area per dose (with a maximum dose of nevirapine 200 mg) administered twice daily. The maximum dose of the extended-release preparation is nevirapine 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 nevirapine 200 mg to 120 mg per m² of body surface area) as the child reaches 8 years of age; rather, the

milligram dose is left static if there are no adverse effects, and the dose is allowed to achieve the appropriate mg per m^2 of body surface area dose as the child grows. Some practitioners dose nevirapine at 150 mg per m^2 of body surface area every 12 hours or nevirapine 300 mg per m^2 of body surface area once daily if using the extended-release preparation (with a maximum of nevirapine 200 mg per dose twice daily for the immediate-release tablets or nevirapine 400 mg once daily for the extended-release tablets) regardless of age, as recommended in the FDA-approved product label.

Dosing Considerations: Lead-In Requirement

Underdosing during the lead-in period may have potentially contributed to the poorer performance of nevirapine in the P1060 trial. This potential for underdosing, which can increase the risk of resistance, has led to re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditionally, nevirapine is initiated with an age-appropriate dose that is given only once daily instead of twice daily (nevirapine 200 mg per m^2 of body surface area in infants aged ≥15 days and children aged <8 years, using the immediate-release preparations) during the first 2 weeks of treatment to allow for the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in nevirapine metabolism.

Studies have previously indicated that there is a potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.[20] The CHAPAS-1 trial[21] randomized 211 children to initiate ART with immediate-release nevirapine 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 standard twice-daily dosing of the immediate-release preparation. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and there was no difference in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated nevirapine without a lead-in dose had a statistically significant increase in the incidence of Grade 2 rash, but the majority of participants were able to continue nevirapine therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 cell count and virologic failure endpoints.

After children had been on nevirapine for 2 weeks, investigators conducted a substudy that examined nevirapine plasma concentrations 3 to 4 hours after a morning dose of nevirapine. Among children aged <2 years, three of 23 children (13%) who initiated at full dose had subtherapeutic nevirapine levels (<3 mg/L) at 2 weeks compared to seven of 22 children (32%) who initiated at half dose ($P = 0.16$). There were no rash events in the substudy group of participants aged <2 years; in the parent CHAPAS study, there was a strong age effect on rash occurrence, with the risk of rash increasing with increasing age. These findings suggest that a lead-in dose may not be necessary in young patients.[22]

Gopalan et al. analyzed nevirapine concentrations in 20 children who had a median age of 9 years and who were just starting a nevirapine-based ART regimen. Subtherapeutic nevirapine concentrations, which were defined as trough concentrations ≤4 mcg/mL, occurred more frequently among children aged ≤8 years (N = 8) than among children aged >8 years (N = 12). Half of the children aged ≤8 years experienced virologic failure by Week 48.[23] The authors of the study suggested that rapid metabolism of nevirapine by CYP2B6 in this particular population may have confounded the results. The small number of participants in this study make the findings difficult to interpret, but the authors recommended a thorough review of nevirapine dose escalation strategies in children. Reinitiating half-dose nevirapine for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes,[24] and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends restarting full-dose nevirapine in children who interrupt therapy for 14 days or less.

Special Considerations for Dosing: Neonates and Premature Infants

For neonates and premature infants (which includes infants with corrected gestational ages of up to 42 weeks), PK data are currently inadequate to formulate an effective ART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for determining the appropriate doses for other ARV drugs. On the basis of PK modeling, an investigational dose of nevirapine 6 mg/kg administered

twice daily has been proposed for full-term infants who receive HIV diagnoses in the first few days of life.[25-29] However, a dose of nevirapine 4 mg/kg per dose twice daily has been chosen for the first week of life in infants born between 34 and 37 weeks' gestation, followed by a nevirapine 6 mg/kg per dose administered twice daily thereafter. Dose adjustments may be required if a premature infant is found to have HIV during the first week of life. The PKs of nevirapine in patients who receive the investigational dose will be evaluated as part of IMPAACT 1115. Initial results from this study indicate that the experimental dosing schedule is safe and provides adequate PKs to maintain trough concentrations of nevirapine >3 mcg/mL in the majority of infants.[30] Providers who are considering initiating treatment in infants aged <2 weeks or in premature infants should contact a pediatric HIV expert for guidance, because the decision about whether to treat an infant and what drugs to use will involve weighing the risks and benefits of using unapproved ART dosing and incorporating case-specific factors, such as exposure to ARV prophylaxis.

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Rilpivirine (RPV, Edurant) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Tablets: 25 mg

Fixed-Dose Combination Tablets:

- [*Complera*] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [*Juluca*] Dolutegravir 50 mg/rilpivirine 25 mg
- [*Odefsey*] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide (TAF) 25 mg

Dosing Recommendations

Neonate and Infant Dose:
- Rilpivirine is not approved for use in neonates or infants.

Children Aged <12 Years:
- Rilpivirine is not approved by the Food and Drug Administration for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

<mark>Child</mark> and Adolescent (Aged <mark>≥12 Years and Weighing ≥35 kg) and Adult Dose:</mark>
- Rilpivirine 25 mg once daily <mark>with a meal</mark> in antiretroviral (ARV) treatment-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 rilpivirine and other ARV drugs in the new regimen.

[*Complera*] Emtricitabine/Rilpivirine/TDF
<mark>Child</mark> and Adolescent (<mark>Aged ≥12 Years and Weighing ≥35 kg) and Adult Dose:</mark>
- One tablet once daily <mark>with a meal</mark> in ARV treatment-naive patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily can also 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 (defined as HIV RNA <50 copies per mL) for ≥6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Complera.

[*Juluca*] Dolutegravir/Rilpivirine
Adult Dose:
- One tablet once daily with a meal as a

Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction/Rash with Eosinophilia and Systemic Symptoms)
- Hepatotoxicity
- Altered ACTH stimulation test of uncertain clinical significance

Special Instructions

- **Do not start** rilpivirine in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- **Do not use** rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- **Do not use** rilpivirine with proton pump inhibitors.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- <mark>H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.</mark>
- Use rilpivirine with caution when coadministering it with a drug that has a known risk of Torsades de Pointes (for more information, see CredibleMeds).
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and

complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) on a stable ARV regimen for ≥6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.

- Not approved for use in children or adolescents (see Simplification of Treatment section below).

[*Odefsey*] Emtricitabine/Rilpivirine/TAF
<mark>Child and</mark> Adolescent (<mark>Aged ≥12 Years and</mark> Weighing ≥35 kg) and Adult Dose:

- One tablet once daily with a meal as initial therapy in ARV treatment-naive patients with HIV RNA ≤100,000 copies per mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies per mL) for ≥6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Odefsey.

additional information about the individual components of the FDC.

Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate.

Rilpivirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

Rilpivirine Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with mild or moderate renal impairment.
- The FDC drugs Complera and Odefsey **should not be used** in patients with creatinine clearance <50 mL/min or <30 mL/min, respectively, or in patients who require dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease, so monitoring for adverse events is especially important in these patients.
- When using Complera, see the TDF section of the guidelines; when using Odefsey, see the TAF section.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Rilpivirine is a cytochrome P450 (CYP) 3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.

- A patient's medication profile should be carefully reviewed for potential drug interactions before rilpivirine is administered.

- Coadministering rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.

- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.

- H2 receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.

- Do not use rilpivirine with proton pump inhibitors.

- Rifampin and rifabutin significantly reduce rilpivirine plasma concentrations; coadministration of

rifampin with rilpivirine is **contraindicated**. For patients who are concomitantly receiving rifabutin, rilpivirine dose should be doubled to 50 mg once daily, taken with a meal.

- In a cohort of adolescent patients, rilpivirine exposure was two to three times greater when rilpivirine was administered in combination with darunavir/ritonavir (DRV/r) than when rilpivirine was administered alone.[1]

Major Toxicities

- *More common:* Insomnia, headache, and rash.

- *Less common (more severe):* Depression or mood changes, suicidal ideation.

- In studies of adults, 7.3% of patients who were treated with rilpivirine showed a change in adrenal function characterized by an abnormal 250-microgram ACTH stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, six out of 30 patients (20%) developed this abnormality.[2] The clinical significance of these results is unknown.

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.

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, rilpivirine used in combination with other ARV agents,[2] the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera),[3] and the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey) are all approved by the Food and Drug Administration (FDA) for use in persons aged ≥12 years and weighing ≥35 kg.[4] The FDC tablet of dolutegravir/rilpivirine (Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.[5]

Efficacy in Clinical Trials

A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be noninferior to efavirenz. Subjects with pretreatment HIV viral loads ≥100,000 copies/mL who received rilpivirine had higher rates of virologic failure than those who received efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral loads ≤100,000 copies/mL.[6-9]

A study of treatment-naive adolescents aged 12 years to 18 years demonstrated that rilpivirine 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. Among 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. Among 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.[10]

Rilpivirine may be used in carefully selected patients. Patients must be able to take rilpivirine 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 select patients who have difficulty swallowing pills but who 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 of age) who acquired

HIV perinatally to receive emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, four were on an NNRTI-based regimen, and one had not received antiretroviral therapy (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 rilpivirine-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 efavirenz-based therapy did not report similar problems while receiving rilpivirine-based therapy.[11]

Pharmacokinetics

The pharmacokinetics (PK), safety, and efficacy of rilpivirine in children aged <12 years have not been established but are under study 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 rilpivirine may be appropriate for use in select children aged <12 years and weighing ≥35 kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to using rilpivirine in this age group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, PAINT TMC278, investigated a 25-mg dose of rilpivirine 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.[10] 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 rilpivirine with a meal. PKs were comparable to those in adults; results are listed in the table below.[12]

Table A. Rilpivirine Pharmacokinetics in Adults and in 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 ± Standard Deviation	2,235 ± 851	2,424 ± 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
C_{0h} (ng/mL)		
Mean ± Standard Deviation	79 ± 35	85 ± 40
Median (Range)	73 (2–288)	79 (7–202)

Source: Adapted from Rilpivirine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202022s011lbl.pdf.[2]

Key to Acronyms: AUC_{24h} = area under the curve after 24 hours; C_{0h} = plasma concentration just prior to next dose; RPV = rilpivirine

In a PK study of youth aged 13 years to 23 years who received rilpivirine,[1] rilpivirine exposure was comparable to the results from PAINT in patients who received 25-mg doses of rilpivirine without DRV/r and substantially higher in those who received 25-mg doses of rilpivirine with DRV/r (area under the curve = 6,740 ng•h/mL). No dose adjustments are currently recommended for adults when rilpivirine is used with DRV/r, where a similar two-fold to three-fold increase in rilpivirine exposure has been reported.[2]

Rilpivirine has been reported to have fewer CNS AEs than efavirenz, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving efavirenz. However, there has been concern that the prolonged half-life of efavirenz might result in residual drug levels that could

have an impact on rilpivirine levels. A Thai study evaluated 20 Thai adolescents 4 weeks after they switched from efavirenz to rilpivirine. The PK parameters of rilpivirine in this study population were comparable with 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 rilpivirine because of AEs.[13]

Simplification of Treatment

Dolutegravir/rilpivirine (Juluca) is an FDC tablet that contains dolutegravir 50 mg and rilpivirine 25 mg. The recently reported results from two trials in adults (SWORD-1 and SWORD-2) support FDA approval of dolutegravir/rilpivirine as a complete regimen for treatment simplification or maintenance therapy in selected 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 dolutegravir or rilpivirine. The participants were randomized to receive dolutegravir/rilpivirine 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] More AEs were reported and more AEs led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.[15] Although dolutegravir/rilpivirine as Juluca is not approved for use in adolescents, the doses of both dolutegravir and rilpivirine in Juluca are approved for use in adolescents as single drugs. 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 currently recommend** the use of Juluca for adolescents and children until more data are available.

Long-Acting, Injectable Rilpivirine

Currently, a long-acting, injectable formulation of rilpivirine is under development as a treatment for adult patients (to be given concurrently with a cabotegravir long-acting injectable).[16-18] An IMPAACT study of the same regimen in adolescents is expected to begin enrolling participants in 2019.

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% (seven of 36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grades 3 and 4 depressive disorders was 5.6% (two of 36 participants).[2]

Six out of 30 adolescents (20%) with a normal adrenocotropic hormone stimulation test at baseline developed an abnormal test during the trial. There were no serious AEs, deaths, or treatment discontinuations attributed to adrenal insufficiency. The clinical significance of abnormal adrenocotropic hormone stimulation tests is not known, but this finding warrants further evaluation.[2]

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Protease Inhibitors (PIs)

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Atazanavir (ATV, Reyataz) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Powder Packet: 50 mg/packet

Capsules: 150 mg, 200 mg, and 300 mg

Generic Formulations

  Capsules: 150 mg, 200 mg, 300 mg

Fixed-Dose Combination Tablets:

- *[Evotaz]* Atazanavir 300 mg/cobicistat 150 mg

Capsules and powder packets are not interchangeable.

Dosing Recommendations

Neonate Dose:

- Atazanavir is not approved for use in neonates and infants aged <3 months. Atazanavir **should not be administered** to neonates due to risks associated with hyperbilirubinemia (kernicterus).

Infant and Child Dose
Powder Formulation:[a]

- The powder formulation must be administered with ritonavir.
- 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	Atazanavir 200 mg (four packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food
15 kg to <25 kg[b]	Atazanavir 250 mg (five packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food

Capsule Formulation:[a]

- Capsules are not approved for use in children aged <6 years or weighing <15 kg.

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 ritonavir boosting)

Special Instructions

- Administer atazanavir with food to enhance absorption.
- Capsules and powder packets **are not interchangeable**.
- Do not open capsules.
- Because atazanavir can prolong the PR interval, use atazanavir with caution in patients with pre-existing 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).
- Atazanavir absorption is dependent on low gastric pH; therefore, when atazanavir is administered with medications that alter gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the atazanavir package insert).
- The plasma concentration, and therefore the therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is coadministered with proton-

Atazanavir 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	Atazanavir/ritonavir[c] 200 mg/100 mg, both once daily with food
≥35 kg	Atazanavir/ritonavir[c] 300 mg/100 mg, both once daily with food

For Treatment-Naive Children and Adolescents Who Do Not Tolerate Ritonavir:

- Atazanavir powder is not an option, since it must be administered with ritonavir. For the capsule formulation, while the Food and Drug Administration (FDA) does not recommend the use of unboosted atazanavir in children aged <13 years, adolescents aged ≥13 years weighing ≥40 kg may be prescribed unboosted atazanavir if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF). However, in order to achieve target drug concentrations, adolescents may require doses of atazanavir that are higher than those recommended for use in adults (see Pediatric Use).
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend use of unboosted atazanavir.

Adolescent and Adult Dose
Treatment-Naive Patients:

- Atazanavir/ritonavir (ATV/r) 300 mg/100 mg once daily with food.[d]
- Atazanavir/cobicistat (ATV/c) is currently not approved by the FDA for use in children or adolescents aged <18 years.
- Atazanavir 400 mg once daily with food. If unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations (see Pediatric Use).
- Emtricitabine/TAF is approved for use with ATV/r in patients weighing ≥35 kg.

Treatment-Experienced Patients:

- ATV/r 300 mg/100 mg once daily with food.[d]
- ATV/c[e] 300 mg/150 mg once daily with food, or coformulated Evotaz once daily with food.
- ATV/c is currently not approved by the FDA

pump inhibitors. ART-naive patients who are receiving proton-pump inhibitors should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before taking boosted atazanavir. Coadministration of atazanavir with proton-pump inhibitors is not recommended in ART-experienced patients.

- Patients with hepatitis B virus or hepatitis C virus infections and patients who had marked elevations in transaminases before treatment may have an increased risk of further elevations in transaminases or hepatic decompensation.
- Atazanavir 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 atazanavir 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 given using an oral dosing syringe.
- Administer ritonavir immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.

Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronyl transferase 1A1.

Atazanavir Dosing in Patients with Hepatic Impairment:

- Atazanavir 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.
- Atazanavir should not be used in patients with severe hepatic impairment.

for use in children aged <18 years.
- Emtricitabine/TAF is approved for use with ATV/r in patients who weigh ≥35 kg.

[*Evotaz*] Atazanavir/Cobicistat

Child and Adolescent Dose:
- ATV/c is currently not approved by the FDA for use in children aged <18 years.

Adult Dose:
- One tablet once daily with food

Atazanavir Dosing in Patients with Renal Impairment:
- No dose adjustment is required for patients with renal impairment.
- Atazanavir should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.

a The mg/kg dosing is higher for the powder packets than for the capsules. In P1020A, children of similar age and size taking atazanavir powder had lower exposures compared with those taking atazanavir capsules.

b Children who weigh ≥25 kg and who cannot swallow atazanavir capsules may receive atazanavir 300 mg (six packets) oral powder plus ritonavir 100 mg oral solution, both administered once daily with food.

c Either ritonavir capsules or ritonavir oral solution can be used.

d Adult patients who cannot swallow capsules may take atazanavir oral powder once daily with food at the same adult dose as the capsules, along with ritonavir.

e See the cobicistat section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat and the combination of cobicistat and TDF.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Atazanavir 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. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. Atazanavir is a weak inhibitor of CYP2C8. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronyl transferase (UGT1A1). Because there is potential for multiple drug interactions with atazanavir, a patient's medication profile should be carefully reviewed for potential drug interactions before atazanavir is administered.

- *Nucleoside reverse transcriptase inhibitors (NRTIs):* Tenofovir disoproxil fumarate (TDF) decreases atazanavir plasma concentrations. Only atazanavir/ritonavir (ATV/r) should be used in combination with TDF. The effect of tenofovir alafenamide (TAF) on unboosted atazanavir is unknown; thus, only ATV/r should be used with TAF.

- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be coadministered to patients who are receiving atazanavir (with or without ritonavir). Efavirenz should not be coadministered with atazanavir in antiretroviral therapy (ART)-experienced patients, but this drug may be used in combination with ritonavir-boosted atazanavir 400 mg in ART-naive adults. Although ATV/r should be taken with food, efavirenz should be taken on an empty stomach, preferably at bedtime.

- *Integrase inhibitors:* Atazanavir is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir. This interaction may not be clinically significant.

- *Absorption:* Atazanavir absorption is dependent on low gastric pH. The dosage for atazanavir should be adjusted when it is administered with medications that alter gastric pH. Guidelines for the appropriate doses of atazanavir to use with antacids, H2 receptor antagonists, and proton-pump inhibitors in adults are complex and can be found on the package insert for atazanavir. No information is available on the

appropriate doses of atazanavir to use in children when the drug is coadministered with medications that alter gastric pH.

- Coadministering cobicistat, 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 cobicistat, atazanavir, and CYP3A4 inducers may lead to lower exposures of cobicistat and atazanavir, a loss of efficacy of atazanavir, and possible development of resistance.[1] Coadministering cobicistat and atazanavir with some antiretroviral (ARV) agents (e.g., with etravirine, with efavirenz in ART-experienced patients, or with another ARV 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 PR interval. Abnormalities in atrioventricular (AV) conduction are generally limited to first-degree AV block, but there have been reports of second-degree AV block. Rash, 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 addition of ritonavir to atazanavir is associated with lipid abnormalities, but to a lesser extent than with other boosted PIs.

- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing 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 atazanavir 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 (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

Atazanavir is approved by the Food and Drug Administration (FDA) for use in infants (aged ≥3 months and weighing ≥5 kg), children, and adolescents.

Efficacy

Studies in treatment-naive adults have shown that ATV/r is as effective as efavirenz and lopinavir/ritonavir (LPV/r) when these drugs are administered with two NRTIs.[2-5] In ACTG A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or raltegravir, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, ATV/r was discontinued more frequently than the other regimens due to toxicity, most often hyperbilirubinemia or gastrointestinal complaints.[6]

P1020 enrolled 195 ART-naive and ART-experienced patients with HIV aged 3 months to 21 years. Capsule and powder formulations and boosted and unboosted regimens 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 atazanavir-based treatment at the final recommended dose. Among them, 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 I and PRINCE II, studied a powder formulation of atazanavir that was administered once daily and boosted with liquid ritonavir.[9-11] One hundred and thirty-four 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 ARV-experienced patients (50%) had HIV RNA <50 copies/mL at Week 48. The median increase from baseline in absolute CD4 T lymphocyte 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 ritonavir boosting, atazanavir can achieve protocol-defined PK targets—but only when used at higher doses (on a mg/kg body weight or mg/m^2 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 520 mg/m^2 per day of the atazanavir capsule formulation to achieve PK targets.[8] Unboosted atazanavir at this dose was well tolerated in those aged <13 years who were able to swallow capsules.[12] The approved dose of atazanavir for adults is 400 mg once daily without ritonavir boosting; however, adolescents aged >13 years required a dose of atazanavir 620 mg/m^2 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 atazanavir, both with and without ritonavir boosting, from IMPAACT/PACTG 1020A are outlined in the table below. When administering unboosted atazanavir to pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.[13] Higher target trough concentrations may be required in PI-experienced patients. IMPAACT P1058, a study of unboosted atazanavir PKs in ART-experienced children, concluded that once-daily atazanavir 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/m^2)[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 AUC/PK parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. TDM 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 to Acronyms: AUC = area under the curve; ATV = atazanavir; PK = pharmacokinetic; RTV = ritonavir; TDM = therapeutic drug monitoring

In the report of the IMPAACT/ PACTG P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m^2 in pediatric subjects when administered with ritonavir.[15] A study of a model-based approach that used atazanavir concentration-time data from three adult studies and one pediatric study (P1020A),[16] along with subsequent additional adjusted modeling,[17] 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

A study of 14 adolescents, aged 12 years to 18 years, suggests that cobicistat is a safe and effective PK

enhancer when used in combination with atazanavir in adolescent patients.[18]

Oral Powder

The unboosted atazanavir 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 to 90,000 ng*hr/mL) were established based on exposures in adults in early studies of unboosted atazanavir. In IMPAACT/PACTG P1020A, children aged 3 months to 2 years who were in the boosted atazanavir powder cohorts and who received a daily dose of atazanavir 310 mg/m² achieved average atazanavir exposures that approached, but did not meet, protocol targets. Variability in exposures was high, especially among the very young children in this age range.[8]

Assessment of the PKs, safety, tolerability, and virologic response of atazanavir oral powder for FDA approval was based on data from two open-label, multicenter clinical trials:

- PRINCE I, which enrolled pediatric patients aged 3 months to <6 years;[9] *and*
- PRINCE II, which enrolled pediatric patients aged 3 months to <11 years.[10]

One hundred and thirty-four 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 atazanavir and two NRTIs. Children received an oral solution that contained atazanavir and ritonavir. Doses were assigned according to the child's weight:

- Weighing 5 kg to <10 kg: Atazanavir 150 mg or atazanavir 200 mg and ritonavir 80 mg
- Weighing 10 kg to <15 kg: Atazanavir 200 mg and ritonavir 80 mg
- Weighing 15 kg to <25 kg: Atazanavir 250 mg and ritonavir 80 mg
- Weighing 25 kg to <35 kg: Atazanavir 300 mg and ritonavir 100 mg

No new safety concerns were identified during these trials. The FDA label includes the following PK parameters that were measured during the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses:

Table B. Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE I and II)[a] versus Capsules in Young Adults[a] and Adults[b]

PK Parameters	PRINCE Trial[b] ATV/r Dose: 150 mg/80 mg Weighing: 5 kg to <10 kg	PRINCE Trial[b] ATV/r Dose: 200 mg/80 mg Weighing: 5 kg to <10 kg	PRINCE Trial[b] ATV/r Dose: 200 mg/80 mg Weighing: 10 kg to <15 kg	PRINCE Trial[b] ATV/r Dose: 250 mg/80 mg Weighing: 15 kg to <25 kg	PRINCE Trial[b] ATV/r Dose: 300 mg/100 mg Weighing: ≥25 kg to <35 kg	Young Adult Study[a]	Adult Study[b]
AUC ng•h/mL Mean[c] (CV% or 95% CI) [N]	32,503 (61%) [20]	39,519 (54%) [10]	50,305 (67%) [18]	55,525 (46%) [31]	44,329 (63%) [8]	35,971 (30,853–41,898) [22]	46,073 (66%) [10]
C_{24h} ng/mL Mean[c] (CV% or 95% CI) [N]	336 (76%) [20]	550 (60%) [10]	572 (111%) [18]	678 (69%) [31]	468 (104%) [8]	578 (474–704) [22]	636 (97%) [10]

[a] The young adults were also receiving TDF.[7]

[b] This information comes from the Reyataz package insert.[10]

[c] Means are geometric means.

Key to Acronyms: ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

While the PK targets were met in these PK studies of atazanavir powder in all patients except those who received ATV/r 150 mg/80 mg in the 5 kg to <10 kg weight band, there were large coefficients of variation,

especially among the youngest patients.

Transitioning from Powder to Capsules

For children who reach a weight ≥25 kg while taking the powder, atazanavir 300 mg powder (six packets) plus ritonavir 100 mg oral solution, both administered once daily with food, may be used. Atazanavir 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

Nine percent of patients enrolled in the IMPAACT/PACTG 1020A trial had a bilirubin ≥5.1 times the upper limit of normal.[12] Nine percent 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 due to 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 study, and all were asymptomatic.

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Darunavir (DRV, Prezista) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Oral Suspension: 100 mg/mL

Tablets: 75 mg, 150 mg, 600 mg, 800 mg

Fixed-Dose Combination Tablets:

- [*Prezcobix*] Darunavir 800 mg/cobicistat 150 mg
- [*Symtuza*] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg

Dosing Recommendations

Note: Darunavir should not be used without a pharmacokinetic (PK) enhancer (boosting agent). Ritonavir may be used as the boosting agent in children and adults; cobicistat should only be used in adults.

Neonate/Infant Dose:

- Darunavir is not approved for use in neonates/ infants.

Child Dose

Aged <3 Years:

- **Do not use darunavir in children aged <3 years or weighing ≤10 kg.** Seizures and death have been observed in infant rats who received darunavir, and 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 treatment-naive or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with darunavir resistance.

Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headache
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

Special Instructions

- Once-daily darunavir 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 there is limited clinical experience with this dosing schedule in this age group.
- Once-daily darunavir **should not be used** if any one of the following resistance-associated substitutions is present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.
- Darunavir must be administered with food, which increases darunavir plasma concentrations by 30%.
- Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergies.
- Pediatric dosing requires coadministration of tablets with different strengths to achieve the recommended doses for each weight band. It is important to provide careful instructions to caregivers when recommending a combination of different-strength tablets.
- Store darunavir tablets and oral suspension at room temperature (25ºC or 77ºF). Suspension

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]	Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)
11 kg to <12 kg[b]	Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL[c])
12 kg to <13 kg[b]	Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL[c])
13 kg to <14 kg[b]	Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL[c])
14 kg to <15 kg	Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL[c])
15 kg to <30 kg	Darunavir 375 mg (combination of tablets or 3.8 mL[d]) plus ritonavir 48 mg (0.6 mL[d])
30 kg to <40 kg	Darunavir 450 mg (combination of tablets or 4.6 mL[d,e]) plus ritonavir (100 mg tablet or powder or 1.25 mL[b])
≥40 kg	Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)

Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; PKs, efficacy, and safety of darunavir/cobicistat is currently under investigation in children aged 12 years to 18 years.

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:
- Darunavir 450 mg (using a combination of tablets) plus ritonavir 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:
- Darunavir 800 mg (using a tablet or combination of tablets) plus ritonavir 100 mg **once daily with food**

Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance:
- Darunavir 800 mg (tablet) plus cobicistat[f] 150 mg (tablet) or the coformulation Prezcobix **once daily with food**

must be shaken well before dosing.
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

Metabolism/Elimination
- Cytochrome P450 3A4 substrate and inhibitor.

Darunavir Dosing in Patients with Hepatic Impairment:
- Darunavir is primarily metabolized by the liver. Caution should be used when administering darunavir to patients with hepatic impairment. Darunavir is not recommended in patients with severe hepatic impairment.

Darunavir Dosing in Patients with Renal Impairment:
- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30–60 mL/min).

Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Experienced Patients with at Least One Mutation Associated with Darunavir Resistance:
- Darunavir 600 mg plus ritonavir 100 mg, both **twice daily with food**
- The use of cobicistat **is not recommended** with darunavir 600 mg twice daily.

[*Prezcobix*] Darunavir/Cobicistat
Child and Adolescent (Aged <18 Years) Dose:
- Prezcobix has not been approved by the Food and Drug Administration (FDA) for use in patients aged <18 years.

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/TAF
Child and Adolescent (Aged <18 Years) Dose:
- Symtuza has not been approved by the FDA for use in patients aged <18 years.

Adult Dose:
- One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed (HIV RNA <50 copies per mL) for at least 6 months with no known substitutions associated with resistance to darunavir or tenofovir.

[a] Once-daily dosing of darunavir is approved by the 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 darunavir 20 mg/kg plus ritonavir 3 mg/kg of body weight per dose, which is higher than the weight-adjusted dose in children with higher weights.

[c] Ritonavir 80 g/mL oral solution.

[d] The volumes for the 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

[e] Some Panel members recommend the FDA-approved dose of once-daily darunavir 675 mg (administered using a combination of tablets) plus ritonavir 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 patients who receive cobicistat.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Metabolism:* Darunavir is primarily metabolized by cytochrome P450 (CYP) 3A4. Both ritonavir and cobicistat are inhibitors of CYP3A4, thereby increasing the plasma concentration of darunavir. Coadministration of darunavir plus ritonavir (DRV/r) or darunavir plus cobicistat (DRV/c) with drugs

that are highly dependent on CYP3A clearance creates potential for multiple drug-drug interactions and may be associated with serious and/or life-threatening events or suboptimal efficacy.

- Coadministration of several drugs, including protease inhibitors and rifampin, is **contraindicated** with DRV/r and DRV/c. A study involving adults with HIV suggested that etravirine may reduce serum darunavir concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent.[1] Before administering darunavir (with or without ritonavir or cobicistat), 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 years to 16 years, both TDF and darunavir 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 may be useful. Data from the IMPAACT protocol P1058A indicate that coadministering once-daily DRV/r with once-daily or twice-daily etravirine in children, adolescents, and young adults aged 9 years to <24 years did not have a significant effect on darunavir plasma concentrations.[3] When DRV/r was coadministered with etravirine twice daily in pediatric patients, target concentrations for both darunavir and etravirine were achieved.[4] Darunavir pharmacokinetics (PKs) were not affected when darunavir was coadministered with rilpivirine in a study of adolescents and young adults.[5] DRV/r coadministration increased rilpivirine exposure two-fold to three-fold; close monitoring for rilpivirine-related adverse events is advisable.

Major Toxicities

- *More common:* Diarrhea, nausea, vomiting, abdominal pain, headache, 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 pre-existing 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 (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

DRV/r is approved by the Food and Drug Administration (FDA) as a component of antiretroviral therapy (ART) in treatment-naive and treatment-experienced children aged ≥3 years.

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 of 21 children (81%) who received DRV/r twice daily had viral loads <50 copies/mL at Week 48.[6,7]

A randomized, open-label, multicenter pediatric trial that evaluated DRV/r twice daily 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.[7,8]

Once-daily DRV/r has been investigated in a small study involving 12 treatment-experienced children aged 6 years 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 months to 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 years 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 ART regimens and had fewer than three darunavir resistance mutations, confirmed by genotypic testing.[6-8] The darunavir area under the curve (AUC_{0-12h}), measured as a percent of the adult AUC value, was 128% overall: 140% in children weighing 10 kg to <15 kg and 122% in children weighing 15 kg to <20 kg.[6-8]

Pharmacokinetics in Children Aged >6 Years

Initial pediatric PK evaluation of darunavir tablets and ritonavir 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.[11] Part 1 of the trial used a weight-adjusted dose of darunavir 9 mg/kg to 15 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily, equivalent to the standard adult dose of DRV/r 600 mg/100 mg twice daily. 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 darunavir 11 mg/kg to 19 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily. This resulted in a darunavir 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), 102% and 114% of the respective PK 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).

A small study that involved 12 treatment-experienced children aged 6 years 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:[12] 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 AUC_{0-24h} geometric mean 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).[15] One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to darunavir; 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)[c]	285/278/119	600 mg/100 mg	54.7–61.7	3,197–3,539

[a] Source: Food and Drug Administration. FDA pharmacokinetics review. 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 FDA pharmacokinetics review 2008. 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 to Acronyms: AUC_{12h} = 12-hour area under the curve; C_{0h} = pre-dose concentration; DRV/r = darunavir/ritonavir

Dosing

Pharmacokinetic Enhancers

Darunavir should not be used without a PK enhancer (boosting agent). Ritonavir may be used as the boosting agent in children and adults; cobicistat should only be used in adults.

A study that enrolled 19 Thai children used the ritonavir 100-mg capsule twice daily as the boosting dose for twice-daily darunavir 375 mg (in children weighing 20 kg to <30 kg), 450 mg (in children weighing 30–40 kg), and 600 mg (in children weighing ≥40 kg).[13] The darunavir exposures with ritonavir 100 mg twice daily were similar to those obtained in the studies with lower (<100 mg) doses of liquid ritonavir.[11,13] The tolerability and PK data from this small study support the use of ritonavir 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 ritonavir formulation. There are no data available on the safety and tolerability of using ritonavir 100 mg tablet or powder formulations in children weighing <20 kg.

Data on the dosing of DRV/c are only available for adult patients.[14] Data on the use of a fixed-dose combination of DRV/c 800 mg/150 mg once daily showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.[15]

Frequency of Administration

In February 2013, the FDA approved the use of once-daily darunavir for treatment-naive children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). 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.[7,16] Currently, there is limited data 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 darunavir resistance. If darunavir and ritonavir are used once daily in children aged <12 years, the Panel recommends conducting a PK evaluation

of plasma concentrations of darunavir 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 darunavir plus ritonavir 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) 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	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] RTV 80 mg/mL oral solution.

[c] The 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.

[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 to Acronyms: 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 darunavir for 2 weeks with PK evaluation 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.[16,17] The DRV/r dose for once-daily use, which was based on PK simulation and which did not include a relative bioavailability factor, was darunavir 40 mg/kg coadministered with approximately 7 mg/kg of ritonavir for children weighing <15 kg, and DRV/r 600 mg/100 mg once daily for children weighing ≥15 kg.[16,17] The PK data obtained from 10 children aged 3 years to 6 years in this substudy (see Table C) 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 years 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, and because of the small set of data used for modeling and the limited amount of data on once-daily DRV/r in children aged <12 years, the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 Years to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Background Therapy

PK Parameter	Children Aged 3 Years to 6 Years (N = 10)[17]	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 to Acronyms: 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 and Weighing ≥40 kg

A substudy of once-daily dosing of DRV/r 800 mg/100 mg demonstrated that darunavir exposures in 12 treatment-naive adolescents (aged 12 years to 17 years and weighing ≥40 kg) were similar to those seen in adults treated with once-daily darunavir (see Table D).[18] 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 darunavir AUC_{24h} and C_{0h} and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those observed in adults with once-daily dosing in another study in which a single dose of darunavir 800 mg with ritonavir 100-mg tablets was administered to 24 subjects with a median age of 19.5 years (range 14 years to 23 years).[19] However, darunavir exposures were slightly below the lower target concentrations in adolescent patients aged 14 years 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 darunavir dose with standard ritonavir 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/mL) Median	C_{0h} (ng/mL) Median
Adolescents Aged 12 Years to 17 Years (mean age 14.6 years)[18]	12	800 mg/100 mg	86.7	2,141
Adolescents and Adults Aged 14 Years to 23 Years (mean age 19.5 years)[19]	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. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017lbledt.pdf

Key to Acronyms: AUC_{24h} = 24-hour area under the curve; C_{0h} = pre-dose concentration; DRV/r = darunavir/ritonavir

The efficacy of once-daily darunavir has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.[10,20]

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Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

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

Dosing Recommendations

Neonatal (Aged <14 Days) Dose:
- There are no data on the appropriate dose of lopinavir/ritonavir (LPV/r) for neonates and no data on the safety of using this drug combination in this age group. **Do not administer** LPV/r to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days due to the risk of toxicities.

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. **Note:** Use of this dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). Also see text for transitioning infants to lower mg per m^2 dose.

Child and Adolescent Dose (Aged >12 Months to 18 Years):
- 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 approximates LPV/r 13 mg/3.25 mg (both per kg body weight) twice daily. For patients weighing ≥15 kg to 45 kg, this dose

Selected Adverse Events

- 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).

Special Instructions

- 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.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- 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.
- Once-daily dosing is not recommended because of considerable variability in plasma

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 treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

- 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 lopinavir 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/dose given twice daily	230 mg/m^2/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, efavirenz, fosamprenavir, or nelfinavir, the Food and Drug Administration (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 nevirapine, efavirenz, fosamprenavir, or nelfinavir; or in patients with three or more lopinavir-associated

concentrations in children aged <18 years and a higher incidence of diarrhea.

- Use of LPV/r once daily is **contraindicated** if three or more of the following lopinavir 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 lopinavir trough concentrations may be required to suppress resistant virus.

Metabolism/Elimination

- Cytochrome P450 3A4 substrate and inhibitor.

LPV/r Dosing in Patients with Hepatic Impairment:

- LPV/r is primarily metabolized by the liver. Use caution when administering lopinavir to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.

- In the coformulation of LPV/r, the ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.

mutations (see Special Instructions for a list of mutations).

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, Efavirenz, Fosamprenavir, or Nelfinavir:
- **Note:** These drugs induce lopinavir metabolism and reduce lopinavir 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 table 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**.

LPV/r Used in Combination with Maraviroc:
- Maraviroc doses may need modification (see the maraviroc section for more information).

Drug Interactions (See also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Lopinavir/ritonavir (LPV/r) is a cytochrome P450 3A4 (CYP3A4) substrate and inhibitor with the potential for multiple drug interactions. Coadministering LPV/r with drugs that induce CYP3A4 may decrease lopinavir plasma concentrations, while coadministering LPV/r with other CYP3A4 inhibitors may increase lopinavir 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 anti-tuberculous drugs are common and may require dose adjustments or a regimen change.

Major Toxicities

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance.[1] Hyperlipidemia, especially hypertriglyceridemia,[2,3] which may be more pronounced in girls than in boys.[4] The higher dose of ritonavir used to boost lopinavir, compared with the dose used with some other

protease inhibitors, may exacerbate these adverse events.

- *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,[5] life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),[6-8] lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3% and ethanol 42.4%.[8] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has also been reported in term newborns treated at birth with LPV/r.[5] 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 antiretroviral (ARV) and anti-tuberculosis medicines in clinical care. In 25 neonates with HIV who received LPV/r solution at a dose of 300 mg/75 mg per m² twice daily, LPV/r was well tolerated and was not associated with any treatment-related adverse events, even in 13 newborns who initiated therapy prior to 42 weeks postmenstrual age at a mean postnatal age of 37 days (with a range of 13 days–61 days).[9]

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

LPV/r is approved by the Food and Drug Administration (FDA) for use in children, including in neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, if no alternatives are available for infants who have not met these age thresholds, some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommend using LPV/r oral solution immediately after birth in combination with careful monitoring of serum osmolality, serum creatinine, liver function enzymes, cardiac function, and electrolytes. Ritonavir acts as a PK enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

Efficacy

Clinical trials involving treatment-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, fosamprenavir, saquinavir/ritonavir, or efavirenz. Studies have also shown that regimens that contain LPV/r plus two NRTIs are superior to regimens that contain nelfinavir and inferior to regimens that contain darunavir.[10-18]

LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and acceptable toxicity.[19-27]

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 m². 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 m² of body surface area.

However, younger children have enhanced lopinavir clearance and need higher doses to achieve lopinavir exposures similar to those seen in adults treated with standard doses. To achieve a C_{trough} similar to that observed in adults, the pediatric dose needs to be increased 30% over the dose that is directly scaled for body surface area. Lopinavir exposures in infants[21,26,28] are compared to those in older children[19] and adults[29] in Table A below.

Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age

	Adults[29]	Children[19]	Children[19]	Infants[a] at 12 Months[26]	Infants at 6 Weeks–6 Months[21]	Infants at 14 Days to <6 Weeks[28]
N	19	12	15	20	18	9
LPV Dose	400 mg	230 mg/m²	300 mg/m²	300 mg/m²	300 mg/m²	300 mg/m²
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] Data were generated in a study that was cited but not reported in a final manuscript. Data in this table came from a personal communication from Edmund Capparelli, PharmD (April 18, 2012).

Note: Values are means; all data comes from studies where none of the participants received NNRTIs as part of their antiretroviral therapy.

Key to Acronyms: AUC = area under the curve; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitors

Models suggest that diet, body weight, and postnatal age are important factors in lopinavir PKs, with improved bioavailability as dietary fat increases during the first year of life[30] and with clearance slowing by age 2.3 years.[31] A study from the United Kingdom and Ireland compared outcomes of LPV/r treatment with either 230 mg per m² of body surface area per dose or 300 mg per m² of body surface area per dose in children aged 5.6 years 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.[32]

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 m² of body surface area per dose twice daily was evaluated in infants aged <6 weeks[28] and infants aged 6 weeks to 6 months.[21] Even at this higher dose, C_{trough} levels were highly variable but 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, lopinavir area under the curve (AUC) was similar to that found in older children.[26] Because infants grow rapidly in the first months of life, it is important to optimize lopinavir dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg per m² of body surface area in older children and adolescents,[22] some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg per m² 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 m² of body surface area when compared to LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily (see Table A above).[18] Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily (when LPV/r is given without nevirapine, efavirenz, fosamprenavir, or nelfinavir), rather than the FDA-approved dose of LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily.

For infants receiving LPV/r 300 mg/75 mg per m² 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 m² of body surface area per dose twice daily dose as they gain weight over time. Some practitioners would continue the infant dose (300 mg per m² 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 lopinavir C_{trough} is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant fosamprenavir or nelfinavir. Higher doses of lopinavir are recommended when the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with LPV/r 230 mg/57.5 mg per m² of body surface area per dose twice daily plus nevirapine, the mean lopinavir C_{trough} was 3.77 ± 3.57 mcg/mL.[19] 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.[19,33] In a study of 15 children with HIV aged 5.7 years to 16.3 years who were treated with LPV/r 300 mg/75 mg per m² of body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in lopinavir trough concentrations. Five of 15 children (33%) had lopinavir 12-hour trough concentrations that were <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.[34] A PK study in 20 children aged 10 years to 16 years who were treated with LPV/r 300 mg/75 mg per m² of body surface area twice daily plus efavirenz 350 mg per m² of body surface area once daily reported only one patient (6.6%) with subtherapeutic lopinavir trough concentrations,[35] perhaps because the trial used an efavirenz dose that was approximately 11 mg/kg body weight[35] instead of the 14 mg/kg body weight dose used in the trial discussed above.[34]

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.[36] 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.[37-40] The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.[40,41] 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, as a greater number of children and adolescents who were on once-daily dosing had viral loads ≥50 copies/mL within 48 weeks.[42]

Dosing and Its Relation to Efficacy

LPV/r is effective in treatment-experienced patients with severe immune suppression,[43,44] although patients with greater prior exposure to ARV drugs may be slower to reach undetectable viral load concentrations[44,45] and may have less-robust CD4 T lymphocyte (CD4) percentage responses.[46]

The relationship between lopinavir exposure and the susceptibility of the HIV-1 isolate (EC_{50}) is a key component of successful treatment. The ratio of C_{trough} to 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.[47-49] 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 m² of body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine, or efavirenz) and LPV/r 480 mg/120 mg per m² of body surface area per dose twice daily (with nevirapine or efavirenz) were safe and tolerable.[22] 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 protease inhibitors.[50] A lopinavir plasma concentration of ≥1 mcg/mL is cited as a minimum target trough concentration,[51-53] but this

concentration may not adequately control viremia in patients with multiple lopinavir mutations.[54,55]

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 of 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.[56,57]

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, C_{max}, and C_{trough} compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 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.[58] In a PK study using a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir C_{trough} measurements.[41]

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.[24,59-63] However, one study did not observe this difference in the effect of LPV/r on CD4 cell count,[64] and another study found that the difference did not persist after a year of therapy.[27] Some studies found no differences between the weight gain of children treated with LPV/r and those treated with efavirenz.[62,65] Switching to an efavirenz-based regimen at or after age 3 years removed the risk of lopinavir-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).[62,63] Bone mineral density improved when children were treated with efavirenz-containing regimens instead of regimens that contained LPV/r.[66]

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Entry and Fusion Inhibitors

Ibalizumab (IBA, Trogarzo)

Maraviroc (MVC, Selzentry)

Ibalizumab (IBA, Trogarzo) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Single-Dose Vial for Intravenous Administration: 200 mg/1.33 mL (150 mg/mL) in a single-dose vial

Dosing Recommendations

Child and Adolescent Dose:
- The safety and efficacy of using ibalizumab in children and adolescents has not been established.

Adult Dose:
- A single loading dose infusion of 2,000 mg administered intravenously (IV) over 30 minutes is followed by a maintenance dose of 800 mg administered IV over 15 minutes every 2 weeks.
- Food and Drug Administration approval is limited to heavily treatment-experienced adults with multidrug-resistant HIV infection who are experiencing treatment failure on their current regimen.
- Ibalizumab is used in combination with other antiretroviral drugs.

Selected Adverse Events
- Diarrhea, dizziness, nausea, rash
- Immune reconstitution inflammatory syndrome
- Potential for immunogenicity in the form of anti-ibalizumab antibodies

Special Instructions
- 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 (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

Ibalizumab is a humanized IgG4 monoclonal antibody that blocks HIV entry into CD4 T lymphocytes (CD4). Based on ibalizumab'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, and depression.[1,2]
- *Less common (more severe):* Immune reconstitution inflammatory syndrome.[1]

Resistance

Ibalizumab resistance mutations will be cataloged on the following websites, which are routinely updated with new findings: the International Antiviral Society-USA (IAS-USA) list of updated resistance mutations

and the [Stanford University HIV Drug Resistance Database](#).

Reduced susceptibility to ibalizumab, as defined by a decrease in maximum percent inhibition, occurs when HIV loses N-linked glycosylation sites in the V5 loop of glycoprotein 120.[1,2]

Phenotypic and genotypic test results showed no evidence of cross resistance between ibalizumab and any approved classes of antiretroviral (ARV) drugs.[3] Ibalizumab exhibits ARV activity against R5-tropic, X4-tropic, and dual-tropic HIV.[3]

Pediatric Use

Approval

Ibalizumab is not approved for use in pediatric patients. Ibalizumab was approved by the Food and Drug Administration 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.[4]

Efficacy in Clinical Trials

Trial TMB-301 was conducted in 40 adults who were 23 to 65 years old, who had body weights ranging from 50 kg to 130 kg, who had resistance to ARV drugs from three classes, who had been treated for at least 6 months on stable ARV regimens and had viral loads >1,000 copies/mL, and who had viral sensitivity to at least one ARV drug.[4,5] Participants continued their current ARV regimens and received a 2,000-mg loading dose of ibalizumab on Day 7 of the study. One week after the loading dose, participants optimized their ART regimens. Participants received ibalizumab 800 mg on Day 21 and every 2 weeks thereafter. At Week 25, 43% of participants achieved suppressed viral loads of <50 copies/mL.[1,5] At Week 48 of an open-label extension study, 24 participants were taking ibalizumab and their optimized ARV regimen. Fifty nine percent of participants (16 of 27 participants) had viral loads <50 copies/mL at 48 weeks.[6,7]

Formulation and Mechanism of Action

Ibalizumab is a recombinant humanized monoclonal antibody that blocks HIV from infecting CD4 cells by binding to domain 2 of the CD4 receptor and interfering with post-attachment steps required for the entry of HIV virus particles into host cells and preventing the viral transmission that occurs via cell-cell fusion.[1,7] Since ibalizumab 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, it does not interfere with CD4-mediated immune functions.

Ibalizumab is formulated in single-dose vials. The solution in the vial has to be diluted in 0.9% Sodium Chloride Injection and administered by intravenous infusion. Inactive ingredients include L-histidine, polysorbate 80, sodium chloride, and sucrose.

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Maraviroc (MVC, Selzentry) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Tablets: 25 mg, 75 mg, 150 mg, and 300 mg
Oral Solution: 20 mg/mL

Dosing Recommendations

Neonate and Infant Dose:

- Maraviroc is not approved by the Food and Drug Administration (FDA) for use in neonates or infants.

Pediatric Dose:

- Maraviroc is approved by the FDA for use in treatment-experienced children aged ≥2 years and weighing ≥10 kg

Recommended Maraviroc Dose for Treatment-Experienced Children Aged ≥2 Years and Weighing ≥10 kg: Tablets or Oral Solution

Weight Band	Twice-Daily Dosing	Oral Solution 20 mg/mL	Tablets
Recommended doses when maraviroc is given with potent cytochrome P450 (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including all protease inhibitors (PIs) except tipranavir/ritonavir (TPV/r)			
10 kg to <20 kg	50 mg	2.5 mL	Two 25-mg tablets
20 kg to <30 kg	75 mg <mark>to 80 mg</mark>	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
<mark>Recommended doses when maraviroc is given with non-interacting drugs,</mark> such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine, enfuvirtide, TPV/r, raltegravir			
10 kg to <20 kg	**Not recommended.** <mark>Data are insufficient to make dosing recommendations for children weighing <30 kg and receiving non-interacting medications.</mark>		
20 kg to <30 kg			
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 maraviroc is given with potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz and etravirine			
Children in all weight bands	**Not recommended.** <mark>Data are insufficient to make dosing recommendations.</mark>		

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

- Maraviroc is recommended for use in patients who only have CCR5-tropic HIV-1. Conduct testing with a HIV tropism assay (see Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines) before using maraviroc to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use maraviroc if CXCR4-tropic or mixed/dual-tropic HIV is present.
- Maraviroc can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering maraviroc to patients with underlying cardiac disease.

Metabolism/Elimination

- Maraviroc is a substrate of CYP3A4. <mark>If a patient is receiving antiretroviral agents or other medications that act as CYP3A inducers or inhibitors, the dose of maraviroc should be adjusted accordingly.</mark>

Recommended Maraviroc Dose for Adults: Tablets

When Coadministered With:	Dose
Potent CYP3A inhibitors (with or without a potent CYP3A inducer), including all PIs except TPV/r	150 mg twice daily
Non-interacting concomitant medications, including NRTIs, enfuvirtide, TPV/r, nevirapine, raltegravir	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz and etravirine	600 mg twice daily

Maraviroc Dosing in Patients with Hepatic Impairment:

- Use caution when administering maraviroc to patients with hepatic impairment; maraviroc concentrations may be increased in these patients.

Maraviroc Dosing in Patients with Renal Impairment:

- There are no data to recommend specific doses of maraviroc in pediatric patients with mild or moderate renal impairment. Maraviroc is **contraindicated** for pediatric patients with severe renal impairment or end-stage renal disease on regular hemodialysis who are receiving potent CYP3A inhibitors.

- Refer to the manufacturer's prescribing information for the appropriate doses to use in adult patients with renal impairment.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Absorption:* Absorption of maraviroc is slightly reduced with ingestion of a high-fat meal. There were no food restrictions in the adult trials (which used the tablet formulation) or in the pediatric trial (which used both the tablet and oral solution formulations) that demonstrated the efficacy, antiviral activity, and safety of maraviroc. Therefore, maraviroc can be given with or without food.

- *Metabolism:* Maraviroc 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 maraviroc is administered; recommended maraviroc doses are based on concomitant medications and their anticipated effect on maraviroc 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 maraviroc 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 maraviroc-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.

Resistance

An HIV tropism assay should be performed before maraviroc is administered to a patient. Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

Pediatric Use

Approval

Maraviroc is approved by the Food and Drug Administration for use in treatment-experienced children aged ≥2 years and weighing ≥10 kg who have CCR5-tropic HIV-1.[1]

Pharmacokinetics and Efficacy

The pharmacokinetics, safety, and efficacy of maraviroc were examined in an international dose-finding and efficacy study (A4001031) that involved treatment-experienced children aged 2 years to <18 years and weighing ≥10 kg who had plasma HIV RNA >1,000 copies/mL. Fifty-one percent of the 103 children who participated in the study had HIV-1 subtype C, 25% had subtype B, and 23% had other subtypes.

In this trial, the maraviroc dose was based on body surface area and the composition of the patient's optimized background therapy. Most participants (90 of 103 participants, or 87%) received maraviroc in combination with potent CYP3A inhibitors, while 10 participants received maraviroc with noninteracting medications and only three participants received maraviroc with CYP3A inducers (without CYP3A inhibitors). The key pharmacologic target (geometric mean $C_{average}$ of >100 ng/mL) was achieved with both the tablet and oral solution formulations of maraviroc.[2]

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 maraviroc-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.[2] The absolute CD4 T lymphocyte cell count and percentage increased in all four subgroups of the study, with an overall median increase of 192 cells/mm³ (interquartile range: 92–352) and 4% (interquartile range: 1–8), respectively.

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Integrase Inhibitors

Bictegravir (BIC)

Dolutegravir (DTG, Tivicay, GSK1349572)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

Bictegravir (BIC) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Note: Bictegravir is only available in a fixed-dose combination tablet.

Fixed-Dose Combination Tablet:

- [*Biktarvy*] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 25 mg

Dosing Recommendations

[*Biktarvy*] Bictegravir plus Emtricitabine plus TAF

Child and Adolescent (Aged <18 Years) Dose:

- Biktarvy has not been approved by the Food and Drug Administration for use in patients aged <18 years.

Children Aged <6 Years and Weighing <25 kg:

- There are currently no data available on the appropriate dose of Biktarvy in children aged <6 years or weighing <25 kg.

Children Aged 6 Years to <12 Years and Weighing ≥25 kg:

- One tablet once daily. This is an **investigational dose** that has only been studied in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable antiretroviral (ARV) regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

Children and Adolescents (Aged 12 to <18 Years and Weighing ≥35 kg):

- One tablet once daily. This is an **investigational dose** that has only been studied 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 substitutions associated with resistance to the individual components of Biktarvy.

Adult (Aged ≥18 Years) Dose:

- One tablet once daily in ARV therapy-naive patients. This dose of Biktarvy can also 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 for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

Selected Adverse Events

- Diarrhea, nausea, headache
- See the Emtricitabine and TAF sections of the Drug Appendix for information about the adverse events that are associated with the use of these drugs.

Special Instructions

- Administer Biktarvy with or without food. See product label for guidance if administering with antacids or iron or calcium supplements.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine or TAF. Severe acute exacerbation of HBV can occur when discontinuing emtricitabine or TAF; therefore, monitor hepatic function for several months after halting therapy with emtricitabine or TAF.
- Biktarvy **is not recommended** for use with other ARV drugs.
- See the emtricitabine and TAF sections of the Drug Appendix for special instructions and additional information about the individual drug components of Biktarvy.

Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.
- Refer to the emtricitabine and TAF sections of the Drug Appendix for more information about the metabolism and elimination of these components of Biktarvy.

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.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- *Metabolism:* Bictegravir is a substrate of cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase (UGT) 1A1. Tenofovir alafenamide (TAF) is a substrate of P-glycoprotein and UGT1A1. Coadministration of Biktarvy and rifampin is **contraindicated**.[1,2]

- *Renal effects:* Bictegravir 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 with no change in glomerular function. Drugs that decrease renal function could reduce clearance of emtricitabine.

- *Absorption:* Administering bictegravir concurrently with antacids lowers the plasma concentrations of bictegravir. This is due to 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 bictegravir. For this reason, Biktarvy should be administered at least 4 hours before or after antacids and iron, calcium, aluminum, and/or magnesium-containing supplements or multivitamins, if Biktarvy is given on an empty stomach. Biktarvy and supplements containing 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 increases were quite mild and did not lead to drug discontinuations in these trials.[2] Bictegravir may cause an increase in creatine kinase concentration.

- *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 (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation. Bictegravir, dolutegravir, and cabotegravir, the "second-generation" INSTIs, have higher barriers to resistance than the first-generation INSTIs raltegravir and elvitegravir[3,4;] and may have more activity against non-B subtypes of HIV.[5]

Pediatric Use

Approval

Bictegravir is not approved for use in children or adolescents. Bictegravir was approved by the Food and Drug Administration in 2018 for use in adults who have no ARV treatment history. It is also approved 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 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of the fixed-dose combination product Biktarvy, which contains 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of TAF.[2]

Efficacy in Clinical Trials

In a short-term Phase 1 study, bictegravir monotherapy at doses of 50 mg or 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 during this study.[6] The efficacy (viral load suppression [VLS] to HIV RNA <50 copies/mL) and safety (incidence of study drug discontinuation [SDD] or death) of Biktarvy were similar to the efficacy and safety of comparator regimens in two Phase 3 randomized trials in treatment-naive adults. VLS occurred in 89% of participants who received coformulated bictegravir/emtricitabine/TAF (BIC/FTC/TAF) 50 mg/200 mg/25

mg (N = 320) and in 93% of participants who received a regimen of dolutegravir 50 mg plus emtricitabine 200 mg plus TAF 25 mg (N = 325). SDD occurred in 1% of participants in both groups. In a separate trial, VLS occurred in 92% of participants who received BIC/FTC/TAF (N = 314) and in 93% of participants who received coformulated abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) 600 mg/50 mg/300 mg (N = 315). SDD was not reported for any of the participants who received BIC/FTC/TAF, though SDD did occur in 1% of participants who received ABC/DTG/3TC.[2,7] Studies that randomized virologically suppressed patients 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. VLS 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). SDD was reported in 2% of participants and 1% of participants, respectively. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (N = 290) achieved VLS, while 89% of participants who continued receiving atazanavir-based or darunavir-based combination ARV regimens (N = 287) achieved VLS. SDD occurred in 1% of participants in both of these groups.[2]

Pharmacokinetics

Pharmacokinetic studies of the adult formulation of Biktarvy, which contains 50 mg of bictegravir, 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. These studies show a higher bictegravir 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). The lower C_{trough} and higher C_{max} in the younger age/lower body weight cohorts suggests more rapid clearance in children and adolescents than adults. Even though the mean serum trough concentrations in the child and adolescent cohorts are similar, there is a higher variability among the serum trough concentrations of the child cohort than among those of the adolescent or adult cohorts. This leads to a lower geometric mean ratio when C_{min} is compared to adult values, and the lower 90% confidence interval (CI) for the child cohort suggests that some patients have quite rapid clearance. This raises the concern that some of the patients in the youngest age/lowest body weight cohort may experience suboptimal troughs (see Table B).

Table A. Bictegravir Pharmacokinetics in Children, Adolescents, and Adults with HIV

PK Parameters	Children Aged 6 Years to <12 Years and Weighing ≥25 kg[8]	Adolescents Aged 12 Years to <18 Years and Weighing ≥35 kg[9]	Adults[2]
Dose (mg)	50	50	50
Dose for the lowest weight in the cohort (mg/kg)	2	1.43	1.25[a]
AUC_{tau} ng•h/mL Mean (CV%)	121,000 (36)	109,668 (31)	102,000 (26.9)
C_{max} ng/mL Mean (CV%)	11,000 (28)	8,087 (30)	6,150 (22.9)
C_{tau} ng/mL Mean (CV%)	2,370 (79)	2,327 (49)	2,610 (35)

[a] This dose was calculated using 40 kg as the lowest weight for adults.

Key to Acronyms: 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; 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 6 Years to <12 Years and Weighing ≥25 kg[8]	50	2	116 (104–130)	177 (162–194)	78.3 (63.4–96.7)
Aged 12 Years to <18 Years and Weighing ≥35 kg[9]	50	1.43	107 (97–118)	130 (119–143)	86 (74–100)

[a] In this table, child and adolescent 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 to Acronyms: AUC_{tau} = area under the concentration time curve over the dosing interval; CI = confidence interval; C_{max} = maximum serum concentration; C_{tau} = trough serum concentration at the end of the dosing interval; GMR = geometric mean ratio; PK = pharmacokinetic

Use of Biktarvy in Adolescents Aged 12 Years to <18 Years

The adult dose formulation of Biktarvy (BIC/FTC/TAF 50 mg/200 mg/25 mg) was administered to adolescents aged 12 years to <18 years who weighed ≥35 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 it was associated with a fall in estimated glomerular filtration rate (eGFR) that was similar to the one seen in adult studies. This decrease in eGFR was related to changes in tubular secretion of creatinine and was not a true change in glomerular function. While the area under the curve (AUC) and C_{max} for bictegravir were similar in adolescents and adults, the mean bictegravir trough in adolescents aged 12 years to <18 years was 2,327 ng/mL (with a CV of 49%); in adults, the mean bictegravir trough was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% CI, 74–100). All 24 participants in the study maintained viral loads <50 copies/mL at Week 24.[9]

Use of Biktarvy in Children Aged 6 Years to <12 Years

BIC/FTC/TAF 50 mg/200 mg/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. Despite a high AUC and C_{max}, the drug combination was well tolerated, with a fall in eGFR similar to that seen in adult studies, which is related to changes in tubular secretion of creatinine and not a true change in glomerular function. There is higher variability among the serum trough concentrations of the child cohort than among those of the adolescent or adult cohorts, and a lower geometric mean ratio when C_{min} is compared to adult values (Table B), although population pharmacokinetic modeling suggests a C_{min} comparable to adult values.[10] All 50 participants in the study had viral loads <50 copies/mL at Week 12, and the 26 participants with data up to Week 24 likewise all had viral loads <50 copies/mL.[8]

The two studies described above were combined and carried to 48 weeks, at which time 74 of 75 participants had viral load <50 copies/mL.[10]

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Dolutegravir (DTG, Tivicay) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablets: 10 mg, 25 mg, and 50 mg

Fixed-Dose Combination Tablets:

- *[Juluca]* Dolutegravir 50 mg/rilpivirine 25 mg
- *[Triumeq]* Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

Dosing Recommendations

Neonate and Infant Dose:

- Dolutegravir is not approved for use in neonates/infants.

Child and Adolescent Dose:

- <mark>No dosing recommendations can be made for children weighing <25 kg.</mark>

- <mark>The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends an investigational dose of dolutegravir 50 mg once daily for children and adolescents weighing ≥25 kg who are antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor [INSTI]-naive) and who are not being treated with uridine diphosphate glucuronyl transferase (UGT) 1A1 or cytochrome P450 3A (CYP3A) inducers.</mark>

- <mark>The Panel's recommended dose is based on interim data from ongoing trials that indicate that using the FDA-approved dose of dolutegravir 35 mg in patients weighing ≥30 kg to 40 kg may result in suboptimal trough concentrations (see text). Using a 50-mg dose also avoids the need to administer two tablets with different strengths (i.e., a 10-mg tablet plus a 25-mg tablet). Dolutegravir is not approved by the Food and Drug Administration (FDA) for use in children weighing <30 kg.</mark>

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) have been reported.

Special Instructions

- Dolutegravir may be taken without regard to meals.
- Dolutegravir 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.
- In patients who have difficulty swallowing tablets whole, 10-mg, 25-mg, and 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 dolutegravir 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).
- When using fixed-dose combination (FDC) tablets that contain dolutegravir, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

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

Population	Recommended Dose
ARV-naive or ARV-experienced/INSTI-naive patients	Dolutegravir 50 mg once daily
ARV-naive or ARV-experienced/INSTI-naive patients who are also receiving one of the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	Dolutegravir 50 mg twice daily
INSTI-experienced patients with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance[a]	Dolutegravir 50 mg twice daily

[a] These patients should receive drug combinations that do not include metabolic inducers when possible.

[*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 substitutions associated with resistance to the individual components of Juluca.

- Juluca is not approved for use in children or adolescents. See the Simplification of Treatment section below.

[*Triumeq*] Abacavir/Dolutegravir/Lamivudine

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

- One tablet once daily

- 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 hypersensitivity.

- The FDA-approved dose for pediatric patients weighing >40 kg is one tablet once daily.

Metabolism/Elimination

- UGT1A1 and CYP3A substrate. Drugs that induce these enzymes and transporters may decrease plasma concentrations of dolutegravir.

Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to a lack of data, dolutegravir is not recommended for use in patients with severe hepatic impairment.

- Dolutegravir decreases tubular secretion of creatinine and increases measured serum creatinine, without affecting glomerular filtration.

Dolutegravir Dosing in Patients with Renal Impairment:

- 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 dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance <30 mL/min), because dolutegravir concentrations will be decreased. The cause of this decrease is unknown.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Dolutegravir is a uridine diphosphate glucuronyl transferase (UGT) 1A1 and cytochrome P450 3A (CYP3A) substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. Because etravirine significantly reduces plasma concentrations of dolutegravir, dolutegravir **should not be administered** with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this

effect on dolutegravir concentrations. Dolutegravir **should not be administered** with nevirapine because of insufficient data on interactions between these drugs.

- Atazanavir is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients who were receiving dolutegravir, patients who also received atazanavir had plasma concentrations of dolutegravir that were two-fold to four-fold higher than those of patients who received other antiretroviral (ARV) drugs.[2]

- Before administering dolutegravir, clinicians should carefully review a patient's medication profile for potential drug interactions.

Major Toxicities

- *More common:* Insomnia and headache.

- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction. Neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note neuropsychiatric adverse effects (AEs) following initiation of dolutegravir-based therapy in adults.[3,4]

- *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 disease and who initiated treatment with integrase inhibitors, particularly dolutegravir.[5,6] This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving integrase inhibitor therapy.

- *Rare:* Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of dolutegravir. One of these cases required liver transplantation.[7,8]

- *Rare:* A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.[9]

- *Rare:* In a prospective surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana, an increased number of neural tube defects was observed among infants born to women who were receiving dolutegravir at the time of conception.[10,11] Further data collection is ongoing, and additional analyses from this study and from other investigations will be required to confirm this potential safety signal. Before patients become sexually active, pediatric and adolescent providers should discuss this potential risk of neural tube defects with patients who are receiving or initiating dolutegravir and their caregivers. Specific recommendations about the initiation and use of dolutegravir in women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (see Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy).

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.

The efficacy of dolutegravir 50 mg twice daily is reduced in patients with the integrase strand transfer inhibitor (INSTI)-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

Pediatric Use

Approval

Dolutegravir is approved by the Food and Drug Administration (FDA) for use in combination with other ARV drugs in children and adolescents weighing ≥30 kg who are treatment-naive or treatment-experienced but INSTI-naive at dolutegravir doses that are lower than the adult dose, although the Panel suggests it can be used in children and adolescents weighing ≥25 kg, see Appendix A, Table 2.[12] The World Health Organization (WHO), however, recommends using dolutegravir at the adult dose of 50 mg

in children weighing ≥25 kg.[13] This recommendation is based on pharmacokinetic (PK) and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY) that are described below. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) agrees with the WHO assessment of these data. The combination tablet abacavir/dolutegravir/lamivudine (Triumeq) is approved for use in children and adolescents weighing ≥40 kg, although the Panel suggests it can be used in children and adolescents weighing ≥25 kg (see Appendix A, Table 2).[14] The combination tablet dolutegravir/rilpivirine (Juluca) is not approved for use in children or adolescents at the time of this review.[15]

Efficacy and Pharmacokinetics

Children and Adolescents Aged ≥12 Years and Weighing ≥40 kg

IMPAACT P1093 is an ongoing open-label trial of dolutegravir in children with HIV. Initial FDA approval of dolutegravir for use in adolescents weighing ≥40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.[16] Intensive PK evaluations were performed on the first 10 participants, nine of whom weighed ≥40 kg and received dolutegravir 50 mg and one of whom weighed 37 kg and received dolutegravir 35 mg. These doses resulted in exposures comparable to those seen in adults receiving 50 mg once daily. Nine of 10 participants achieved HIV RNA concentrations <400 copies/mL at Week 4 (optimal background therapy was added 5 days–10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% of participants had achieved HIV RNA concentrations <50 copies/mL. No safety or tolerability concerns were identified. By Week 144, 39% and 30% of participants had achieved HIV RNA concentrations <400 copies/mL and <50 copies/mL, respectively. All participants who experienced virologic failure were nonadherent.

Additional long-term safety and efficacy data for this age/weight group comes from a French, retrospective, multicenter cohort study that evaluated 50 adolescents who initiated dolutegravir-based ART. Of 17 adolescents who were virologically suppressed at the time of dolutegravir-based treatment, 14 (82%) maintained suppression and three had transient viral rebound prior to re-achieving a plasma viral load <50 copies/mL. Of the 33 viremic adolescents who initiated dolutegravir, 19 (58%) achieved sustained virologic success. Overall, 66% of patients achieved sustained virologic suppression and 78% had undetectable plasma viral load by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and had more frequently detectable viremia in the 6 months prior to dolutegravir initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued dolutegravir-based treatment because of a significant AE (dizziness and sleep disturbance).[17]

Another cohort of adolescents in Barcelona received the fixed-dose combination (FDC) product abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (Triumeq). Of the twelve patients reported, 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 due to suboptimal adherence. Of note, patients complained about the size of the tablet and six reported having to crush or split the tablet in order to swallow it (see Appendix A, Table 2).[18]

Children and Adolescents Aged <12 Years

The ODYSSEY trial, conducted by the Pediatric European Network for the Treatment of AIDS (PENTA) is enrolling both treatment-naive and treatment-experienced pediatric patients in the European Union (EU), Thailand, and several African countries; this trial initially evaluated doses approved by the European Medicines Agency (EMA; see below). A total of 674 children aged <18 years were enrolled; 282 children started dolutegravir as first-line therapy and 392 started dolutegravir as second-line therapy.[19] Nested PK substudies within ODYSSEY are also evaluating simplified pediatric dosing that aligns with WHO-recommended weight bands. PK data are available from a cohort of children weighing >25 kg who switched to the 50-mg dolutegravir tablet (N = 27). Children weighing ≥25 kg who received the 50-mg, film-coated tablet achieved exposures similar to those seen in adults who received the same dose. When given to children weighing 14 kg to <25 kg, the dolutegravir 25-mg, film-coated tablet resulted in drug exposures that were lower than the target exposure for adults, particularly C_{trough}. The median C_{trough} was lower in the 20 kg

to <25 kg group than in the 14 kg to <20 kg group. Higher doses are currently under study in these weight bands, and doses for lower weight bands in the study have been adjusted accordingly.[20,21]

In addition, a younger cohort of children aged ≥6 years to <12 years had PK assessment and remains in longer-term follow up in IMPAACT P1093, with those weighing ≥30 kg to <40 kg receiving the 35 mg dose and those weighing ≥40 kg receiving the 50 mg dose. At 48 weeks, data from 23 participants demonstrated a favorable safety profile, adequate PKs, and virologic efficacy, with HIV RNA concentrations of <50 copies/mL achieved in 17 of 23 participants (74%).[16,22] These data led to the FDA approval of the lower-strength, film-coated dolutegravir tablets at a dose of 35 mg for use in children with HIV who weigh ≥30 kg to <40 kg. The FDA did not approve dosing for children weighing <30 kg because the available PK data in lower weight bands were minimal and the observed C_{trough} concentrations were lower than expected.

The EMA used the same data to inform population PK modelling and simulation analyses to approve the lower-strength, film-coated dolutegravir tablets for use in children aged ≥6 years and weighing ≥15 kg.[23] The EMA approved doses of dolutegravir 20 mg for children weighing 15 kg to <20 kg and doses of 25 mg for those weighing 20 kg to <30 kg. As noted above, evaluation of these doses during the ODYSSEY study indicated that many children failed to achieve adequate trough concentrations. The Panel agrees with the WHO dosing recommendation of dolutegravir 50 mg (as the film-coated tablet) for pediatric patients weighing ≥25 kg and does not recommend use of dolutegravir in children weighing <25 kg. Further data are needed to determine an appropriate dose for this weight group.

The safety and effectiveness of the EMA dosing strategy was evaluated in a cohort of children aged 6 years to <18 years in the United Kingdom and Ireland who were followed during the CHIPS study. Between January 2014 and March 2018, 174 children in the cohort received dolutegravir at the EU-licensed doses. Of these 174 children, 53% were female, 91% had perinatally acquired HIV, and the median age was 15.5 years at the initiation of dolutegravir (interquartile range: 13.5 years–16.7 years). Only 6% of the cohort was treatment-naive, and 38% had previous exposure to three classes of ARVs. Overall, nine participants (5%) discontinued dolutegravir; three discontinued because of toxicity, three because an alternative regimen was available, and three for other reasons or missing reasons. Viral suppression was reported in 80 of 95 participants (84%) who remained on dolutegravir for 6 months, and viral suppression was reported in 41 of 49 participants (84%) who remained on dolutegravir for 12 months. Median changes in CD4 T lymphocyte cell counts were -9 cells/mm^3 at 6 months (N = 81) and +47 cells/mm^3 at 12 months (N = 41) of dolutegravir treatment.[24]

Children Aged <6 Years Who Are Not Able to Swallow Tablets

IMPAACT P1093 also investigated the use of solid, oral-dosage forms of dolutegravir in patients aged as young as 4 weeks. Among the initial doses studied, a dolutegravir granule formulation was well tolerated; area under the curve (AUC_{24h}) values were within target ranges, but C_{24h} levels were below target ranges.[25] In response to stakeholder feedback, the manufacturer decided to stop development of the granules and instead developed a dispersible tablet formulation. The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,[26] so doses studied using the dispersible tablet cannot be directly compared to those using the film-coated tablet. The first presentation of the data on dolutegravir dispersible tablets reported that three age cohorts of 10 patients (≥4 weeks to <6 months, ≥6 months to <2 years, and ≥2 years to <6 years) received protocol-defined, weight-based dosing using combinations of 5-mg, dispersible tablets. While target AUC_{24h} and C_{24h} levels were achieved in the youngest cohort, C_{24h} levels were low in children 6 months to <6 years of age. The dispersible tablet formulation was well-tolerated by all age groups. Higher doses are being evaluated in some age/weight groups.[27]

Simplification of Treatment

Two trials in adults (SWORD-1 and SWORD-2) supported the approval of a dolutegravir 50 mg/rilpivirine 25 mg FDC tablet (Juluca) as a complete regimen for treatment simplification or maintenance therapy in selected 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 who had no history of treatment failure or evidence of resistance mutations. The participants were randomized to either receive dolutegravir/rilpivirine or to continue

their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.[28] More AEs were reported and led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.[29] Although Juluca is not approved for use in adolescents, Juluca contains doses of dolutegravir and rilpivirine that are approved for use in adolescents as drugs. The Panel usually endorses the use of adult formulations in adolescents, and this product 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 Juluca in adolescents and children until more data are available.

Crushing Film-Coated Tablets for Administration

In patients who have difficulty swallowing whole tablets, 50-mg tablets (and 10-mg or 25-mg tablets, should they need to be used) 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] 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.[30]

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Elvitegravir (EVG) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: https://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Tablet: Discontinued by the manufacturer. Elvitegravir is only available in fixed-dose combination (FDC) tablets.

Fixed-Dose Combination Tablets:

- [*Genvoya*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg
- [*Stribild*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg

Dosing Recommendations

[*Genvoya*] Elvitegravir/Cobicistat/Emtricitabine/TAF

Child (Weighing <25 kg) Dose:

- There are no data on the appropriate dose of elvitegravir in Genvoya for children weighing <25 kg.

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

- One tablet once daily with food

[*Stribild*] Elvitegravir/Cobicistat/Emtricitabine/TDF

Child and Adolescent (Weighing <35 kg) Dose:

- There are no data on the appropriate dose of elvitegravir in Stribild for children or adolescents weighing <35 kg.

Adolescent (Weighing ≥35 kg and Sexual Maturity Rating [SMR] 4 or 5) and Adult Dose:

- One tablet once daily with food

Note: Stribild and Genvoya are approved by the Food and Drug Administration for use in antiretroviral (ARV)-naive patients or 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 substitutions associated with resistance to the individual components of Genvoya or Stribild.

Selected Adverse Events

Elvitegravir-Associated Adverse Events:

- Diarrhea

Stribild-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

TDF-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.

Genvoya-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

TAF-Specific Adverse Events:

- Increased levels of low-density lipoprotein cholesterol and total cholesterol.

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

- Administer both Genvoya and Stribild with food.
- <mark>Separate elvitegravir dosing from antacids and iron, calcium, aluminum, and/or magnesium-containing supplements and multivitamins by at least 4 hours.</mark>
- When using Stribild, which contains TDF, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 months 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 emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with emtricitabine, TDF, or TAF.

Metabolism/Elimination

- Elvitegravir is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.
- Elvitegravir should only be used with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the TDF and TAF sections for further details.
- 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. Emtricitabine and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.
- Genvoya **should not be initiated** in patients with estimated CrCl <30 mL/min.
- Stribild and Genvoya **should be not used** in patients with severe hepatic impairment.

Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- *Absorption:* Elvitegravir plasma concentrations are lower with concurrent administration of divalent cations because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Because of this, <mark>Stribild and</mark> Genvoya should be administered at least 4 hours before or after administering antacids and iron, calcium, aluminum, and/or magnesium-containing supplements and multivitamins.<mark>[1]</mark>

- *Metabolism:* Stribild and Genvoya contain elvitegravir and cobicistat. Elvitegravir is metabolized predominantly by cytochrome P450 (CYP) 3A4, secondarily by uridine diphosphate glucuronyl transferase 1A1/3, and by oxidative metabolism pathways. Elvitegravir is a moderate inducer of CYP2C9. Cobicistat is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits the adenosine triphosphate-dependent transporters BCRP and P-glycoprotein and the organic anion-transporting polypeptides OATP1B1 and OATP1B3. There is potential for multiple drug interactions when using both elvitegravir and cobicistat. <mark>Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain ritonavir, due to the similar effects of cobicistat and ritonavir on CYP3A4 metabolism.</mark>

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (TDF) or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided when using Stribild. <mark>Cobicistat inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL in adults. Significant increases in serum creatinine levels may represent renal toxicity and should be evaluated.</mark>

Major Toxicities

- *More common:* Nausea, diarrhea, and 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 emtricitabine. 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; 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.

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. There is phenotypic cross-resistance between elvitegravir and raltegravir.[2]

Pediatric Use

Approval

Stribild (which contains elvitegravir, cobicistat, emtricitabine, and TDF) is approved by the Food and Drug Administration (FDA) for use in children and adolescents aged ≥12 years and weighing ≥35 kg.[3,4] <mark>However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting the use of Stribild in adolescents with sexual maturity ratings (SMRs) of 4 or 5 due to concerns about decreased BMD in pre-pubertal patients.</mark>

Genvoya (which contains elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide [TAF]) is

approved by the FDA for use in children and adolescents weighing ≥25 kg with any SMR.[5]

Efficacy in Clinical Trials

A combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be noninferior to a regimen of efavirenz/emtricitabine/TDF[6] and noninferior to a regimen of atazanavir/ritonavir (ATV/r) plus emtricitabine/TDF in adults at 144 weeks of treatment.[7] In two studies, 1,733 adults were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TAF. After 48 weeks, those receiving elvitegravir/cobicistat/emtricitabine/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%; $P < 0.0001$).[8]

Formulations

Elvitegravir is an INSTI that is metabolized by CYP3A4. Elvitegravir must be used in the FDC products Stribild[4] or Genvoya,[5] both of which contain cobicistat (see below). Cobicistat itself does not have antiretroviral (ARV) activity, but it is a CYP3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to ritonavir.[9]

Stribild is approved by the FDA as a complete antiretroviral therapy (ART) regimen for ARV-naive adults and adolescents with HIV aged ≥12 years and weighing ≥35 kg. It can also be used to replace the current ART regimen in those 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 substitutions associated with resistance to the individual components of Stribild.[4] Trials have shown that Stribild is noninferior to regimens of emtricitabine plus TDF plus ATV[10,11] or emtricitabine plus TDF plus efavirenz.[12,13] Cobicistat inhibits renal tubular secretion of creatinine, and serum creatinine will often increase soon after initiation of treatment with Stribild. Therefore, creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, even though the actual GFR might be only minimally changed.[14] People who experience a confirmed increase in serum creatinine levels >0.4 mg/dL from baseline 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.[4] Careful periodic evaluation of renal function is warranted, because Stribild contains TDF, which has been associated with renal toxicity. This nephrotoxicity may be more pronounced in patients with pre-existing renal disease.[4]

Genvoya is approved for use in children weighing ≥25 kg. Genvoya is approved by the FDA as a complete ART regimen in children with HIV who are ARV-naive. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (i.e., HIV RNA <50 copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.[5] Because Genvoya contains TAF instead of TDF, Genvoya is expected to have a lower risk of bone and renal toxicity than Stribild. Two studies of adults have shown that fewer cases of renal and bone toxicity occurred among patients who received Genvoya than among those who received Stribild. After 48 weeks of treatment, participants who were treated with Genvoya had significantly smaller increases in levels of serum creatinine, less proteinuria, and smaller decreases in BMD at the spine and hip than participants treated with Stribild.[8] In children aged ≥6 years and weighing ≥25 kg who were treated with TAF-containing regimens, no clinically relevant changes were observed in BMD, levels of serum creatinine, and estimated GFR between baseline and 48 weeks of treatment.[15]

Coadministration of Elvitegravir, Cobicistat, and Darunavir

The combination of Stribild or Genvoya plus darunavir has the potential to provide a low pill burden regimen for treatment-experienced individuals. However, an unfavorable drug interaction between elvitegravir/cobicistat and darunavir is possible and the available data on the magnitude of the interaction are conflicting. There are also conflicting data on the efficacy of the combination in adults.[16-22]

The most rigorous drug interaction study, performed in HIV-seronegative adults, found 21% lower darunavir

trough concentrations and 52% lower elvitegravir trough concentrations with darunavir 800 mg plus elvitegravir/cobicistat 150 mg/150 mg once daily compared to administration of either darunavir/cobicistat 800/150 once daily or elvitegravir/cobicistat 150 mg/150 mg once daily alone.[16] The actual trough values were 1,050 ng/mL for darunavir and 243 ng/mL for elvitegravir.

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 on 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 darunavir 800 mg once daily.[20] Intensive PK sampling was performed in 15 of these patients (17%). Mean darunavir and elvitegravir troughs were 1,250 ng/mL and 464 ng/mL, respectively.

Given the uncertainly around the true magnitude of the drug interaction and absence of data in children, this combination should be used with caution in children.

Use of Elvitegravir as Genvoya or Stribild in Children Weighing <25 kg

Neither Genvoya nor Stribild is approved to treat children weighing <25 kg.[4,5] An ongoing study is evaluating the use of Genvoya in children aged <6 years and weighing <25 kg.

Use of Elvitegravir as Genvoya in Children Aged 6 Years to <12 Years

Genvoya is approved by the FDA to treat children with any SMR who weigh ≥25 kg;[5] this approval is based on 24 weeks of data from a study in 23 children.[23] 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. There were no study discontinuations due to medication toxicity, but at Week 24 the participants' CD4 T lymphocyte (CD4) cell counts had decreased by median of 130 cells/mm^3 (with a range of -472 cells/mm^3 to 266 cells/mm^3), and CD4 percentages decreased by a median of 2.1% (with a range of -8.4% to 5.9%). After 48 weeks of follow-up, the CD4 cell count decline from baseline was -90 cells/mm^3. The mechanism for the reduction in CD4 cells is unclear, and this reduction has only been observed 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 there was no association between plasma exposures of the four components of Genvoya and CD4 cell counts.[24] Stribild is not approved by the FDA for use in children weighing <35 kg.

Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 Years to 18 Years

Studies of the adult dosage formulations of Stribild and Genvoya used 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.[4] Genvoya is preferred over Stribild when treating children with SMRs 1 to 3, as Genvoya carries a lower risk of renal and bone toxicity than Stribild.[5]

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Raltegravir (RAL, Isentress) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf/

Formulations

Tablet: 400 mg (film-coated poloxamer tablet)

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 final concentration of 10 mg/mL.

Note: Film-coated tablets, chewable tablets, and oral suspension **are not interchangeable**.

Dosing Recommendations

Note: No dosing information is available for preterm infants or <mark>infants weighing <2 kg at birth</mark>. (See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12 for information about using raltegravir for the prevention of perinatal HIV transmission).

Neonate (Weighing ≥2 kg) Dose

Raltegravir Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks: Neonates Aged ≥37 Weeks and Weighing ≥2 kg

Body Weight	Volume (Dose) of Suspension
Birth to 1 Week of Age: Once-Daily Dosing	**Approximately 1.5 mg/kg/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/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

Note: If the mother has taken raltegravir 2 hours to 24 hours prior to delivery, the neonate's first dose should be delayed until 24 hours to 48 hours after birth.

Note: Metabolism by uridine diphosphate glucuronyl transferase (UGT1A1) is low at birth and increases rapidly during the next 4 to 6 weeks of life.

Infant and Child (Weighing ≥3 kg to <20 kg) Dose

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

- Raltegravir can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any raltegravir formulations.
- Significant drug interactions are more likely to occur when the raltegravir HD formulation is used once daily. **The following drugs should not be coadministered:** calcium carbonate, 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 tablets. See specific recommendations for proper dosing of different formulations.

Raltegravir Oral Suspension Dosing Table for Patients Aged ≥4 Weeks[a]

Body Weight	Volume (Dose) of Suspension to be Administered Twice Daily
3 kg to <4 kg	2.5 mL (25 mg)
4 kg to <6 kg	3 mL (30 mg)
6 kg to <8 kg	4 mL (40 mg)
8 kg to <11 kg	6 mL (60 mg)
11 kg to <14 kg	8 mL (80 mg)
14 kg to <20 kg	10 mL (100 mg)

[a] The weight-based dosing recommendation for the oral suspension is based on approximately raltegravir 6 mg/kg per dose twice daily.

Note: The maximum dose of oral suspension is 10 mL (raltegravir 100 mg) twice daily.

Note: For children weighing 11 kg to 20 kg, either oral suspension or chewable tablets can be used.

Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

Children Weighing ≥11 kg:

- Weighing <25 kg: Chewable tablets twice daily. See table below for chewable tablet dose.
- Weighing ≥25 kg: Raltegravir 400-mg, film-coated tablet twice daily **or** chewable tablets twice daily. See table below for chewable tablet dose.

Children and Adolescents Weighing ≥50 kg:

- Two raltegravir 600-mg HD tablets (1,200 mg) once daily
- This dose is for treatment-naive or virologically suppressed patients who are on an initial dose of raltegravir 400 mg twice daily.
- See the Approval section under the Pediatric Use heading below for more information.

Chewable Tablet Dosing Table[a]

Body Weight	Dose	Number of Chewable Tablets
11 kg to <14 kg	Raltegravir 75 mg twice daily	Three 25-mg tablets twice daily
14 kg to <20 kg	Raltegravir 100 mg twice daily	One 100-mg tablet twice daily
20 kg to <28 kg	Raltegravir 150 mg twice daily	One and a half 100-mg tablets[b] twice daily
28 kg to <40 kg	Raltegravir 200 mg twice daily	Two 100-mg tablets twice daily
≥40 kg	Raltegravir 300 mg twice daily	Three 100-mg tablets twice daily

[a] The weight-based dose recommendation for the chewable tablet is based on approximately raltegravir 6 mg/kg per dose twice daily.

- The chewable tablets should be stored in the original package with a desiccant to protect them from moisture.
- The chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- The oral suspension comes in a kit that includes mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document. Each foil packet is single-use and contains 100 mg of raltegravir, which will be suspended in 10 mL of water for a final concentration of raltegravir 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.

Metabolism/Elimination

- UGT1A1-mediated glucuronidation

Raltegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients who have mild-to-moderate hepatic insufficiency and are receiving twice daily dosing of raltegravir.
- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving either raltegravir 1,200 mg once daily or 400 mg twice daily.
- No studies have been conducted on the use of raltegravir HD in patients with hepatic impairment. Therefore, administration of raltegravir HD **is not recommended** in patients with hepatic impairment.
- The effect of severe hepatic impairment on raltegravir pharmacokinetics has not been studied.

Raltegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with any degree of renal impairment.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* The major route of raltegravir elimination is mediated through glucuronidation by uridine diphosphate glucuronyl transferase (UGT1A1).

- Coadministering raltegravir with inducers of UGT1A1, such as rifampin and tipranavir, may result in reduced plasma concentrations of raltegravir. Inhibitors of UGT1A1, such as atazanavir, may increase plasma concentrations of raltegravir. No dosing modifications are recommended when raltegravir is coadministered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r). However, raltegravir HD tablets **should not be coadministered** with TPV/r (see the text below).

- In adults, an increased dose of raltegravir is recommended when it is coadministered with rifampin. For adults receiving rifampin, the recommended raltegravir dose is 800 mg twice daily. **Do not coadminister** rifampin with once-daily raltegravir HD tablets. In children aged 2 years to <12 years who had tuberculosis/HIV coinfection and who were taking rifampin, raltegravir 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 raltegravir plasma concentrations and **should not be coadministered** with raltegravir.

- Significant drug interactions may be more likely to occur with raltegravir HD once daily. C_{trough} concentrations in adults are approximately 30% lower with raltegravir HD 1,200 mg once daily than with raltegravir 400 mg twice daily. A lower C_{trough} increases the potential for clinically significant drug interactions with interfering drugs that decrease raltegravir exposure and further lower C_{trough}. In addition to aluminum-containing and magnesium-containing antacids, the following drugs **should not be coadministered** with the raltegravir HD formulation: calcium carbonate, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug-metabolizing enzymes on raltegravir is unknown; coadministration with phenytoin, phenobarbital, and carbamazepine **is not recommended**.

- Before administering raltegravir, clinicians should carefully review a patient's medication profile for potential drug interactions with raltegravir.

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 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 raltegravir with caution in patients who are receiving medications associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with prior history. 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 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

Raltegravir is an integrase strand transfer inhibitor (INSTI) that is approved by the 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 raltegravir HD, which allows for once-daily dosing, for use in children and adolescents weighing ≥40 kg. However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using raltegravir HD in children weighing ≥50 kg, since there are no clinical data on the use of raltegravir HD once-daily dosing in children or adolescents weighing <50 kg.

Efficacy in Clinical Trials

Raltegravir 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 raltegravir-containing regimen and an efavirenz-containing regimen. At 48 weeks, raltegravir was noninferior to efavirenz. However, more patients discontinued efavirenz during the longer follow-up periods of 4 and 5 years, and raltegravir was found to be virologically and immunologically superior compared to efavirenz.[4-6] Results from SPRING-2 study in treatment-naive adults showed that raltegravir and dolutegravir were equally effective and had similar safety profiles.[7] ACTG A5257 compared raltegravir to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but raltegravir had better tolerability.[8]

Raltegravir 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 years to 18 years who were mostly treatment-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 raltegravir. Infants and toddlers aged ≥4 weeks to <2 years were also enrolled in IMPAACT P1066 and received treatment with raltegravir oral suspension. At Weeks 24 and 48, 61% of the participants (14 of 23 infants and toddlers) had HIV viral loads <400 copies/mL.[9-11] FDA approval for the use of raltegravir in infants as young as 4 weeks of age was based on the results of this study.

The ONCEMRK study compared raltegravir 1,200 mg once daily (taken as two 600-mg HD tablets) to raltegravir 400 mg twice daily in treatment-naive adults. Once-daily dosing of raltegravir 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 raltegravir regimen. While the HD tablets are approved by the FDA for use in children weighing ≥40 kg, the Panel **does not recommend** using HD tablets in children weighing <50 kg (see below).

Efficacy and Pharmacokinetics of Once-Daily Dosing in Children and Adults

Raltegravir 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 raltegravir 800 mg once daily or raltegravir 400 mg twice daily. After 48 weeks of treatment, the percentage of patients who achieved HIV RNA viral loads <50 copies/mL was 83% in the once-daily group compared to 89% in the twice-daily group. Patients in the once-daily arm with C_{trough} concentrations below 45 nM were at the greatest 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 raltegravir trough plasma concentrations above 45 nM is important for efficacy.[12,13]

Once-daily dosing with raltegravir 1,200 mg was found to be as effective as dosing with raltegravir 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either raltegravir 1,200 mg once daily (taken as two 600-mg tablets) or raltegravir 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. There was no difference in discontinuation rates due to side effects between the two groups.[14] In May 2017, once-daily dosing of raltegravir 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 raltegravir 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 raltegravir HD tablets predict that this dosing schedule will produce drug exposures that are similar to those observed in adult patients during ONCEMRK.[3,15]

Dosing with three 400-mg tablets once daily and dosing with two 600-mg 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 raltegravir HD tablets than in those taking raltegravir 400 mg twice daily. Because of this, the potential for significant drug interactions is greater with once-daily dosing, as interfering drugs that decrease drug exposure may further decrease C_{trough}. C_{max} is approximately six times higher in patients receiving raltegravir 1,200 mg once daily than in those receiving raltegravir 400 mg twice daily, with a two-fold higher area under the curve (AUC).

While modeling and simulations for pediatric patients may indicate that PK targets are met using the once-daily raltegravir 1,200 mg dose, safety cannot be extrapolated for children weighing <50 kg. There were six children in IMPAACT P1066 who had drug exposures that were similar to those observed in ONCEMRK, but all six children weighed >50 kg. Potential dose-related central nervous system toxicities, such as insomnia or hyperactivity, might occur in children exposed to very high concentrations of raltegravir.[3] The Panel recommendations differ from those of the FDA because there are no clinical data on once-daily dosing with raltegravir HD tablets in children or adolescents weighing <50 kg. While the FDA has approved the use of once-daily dosing with raltegravir HD tablets in children weighing ≥40 kg, the Panel recommends using once-daily dosing with raltegravir HD tablets only in children and adolescents who weigh ≥50 kg.

Efficacy and Pharmacokinetics in Children

IMPAACT P1066 evaluated the PKs, safety, and efficacy of raltegravir in children aged 4 weeks to 18 years. A description of the study cohorts and a summary of the PK parameters can be found in Tables A and B.[10,11]

Table A. Summary of IMPAACT P1066 Cohorts and Participation[10,11]

Age	Cohort	Formulation	Number of Participants Who Received the Final Recommended Dose
12 Years to <19 Years	I	Film-coated tablet	59
6 Years to <12 Years	IIA	Film-coated tablet	4
6 Years to <12 Years	IIB	Chewable tablet	13
2 Years to <6 Years	III	Chewable tablet	20
6 Months to <2 Years	IV	Oral suspension	14
4 Weeks to <6 Months	V	Oral suspension	12

Table B. Summary of IMPAACT P1066 PK Results by Cohort[10,11]

Age	Cohort	Formulation	Intensive PK	Mean Dose	GM (CV%)[a] AUC$_{0-12h}$ µMxhr	GM (CV%)[b] C$_{12h}$ nM
12 Years to <19 Years	I	Film-coated tablet	11	9.3 mg/kg	15.7 (98%)	333 (78%)
6 Years to <12 Years	IIA	Film-coated tablet	11	13.5 mg/kg	15.8 (120%)	246 (221%)
6 Years to <12 Years	IIB	Chewable tablet	10	6.5 mg/kg	22.6 (34%)	130 (88%)
2 Years to <6 Years	III	Chewable tablet	12	6.2 mg/kg	18.0 (59%)	71 (55%)
6 Months to <2 Years	IV	Oral suspension	8	5.9 mg/kg	19.8 (34%)	108 (52%)
4 Weeks to <6 Months	V	Oral suspension	11	5.7 mg/kg	22.3 (40%)	117 (68%)

[a] PK targets for Cohorts I–III: AUC$_{0-12h}$ 14–25 µM*hr (6–11 mg*h/L); C$_{12h}$ nM ≥33 nM (14.7 ng/mL)

[b] PK targets for Cohorts IV–V: AUC$_{0-12h}$ 14–45 µM*hr (6–20 mg*h/L); C$_{12h}$ nM ≥75 nM (33.3 ng/mL)

Key to Acronyms: AUC = area under the curve; C$_{12h}$ = concentration at 12 hours (trough); CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic

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 raltegravir in antiretroviral treatment (ART)-experienced children and adolescents with HIV aged 2 years to 18 years. Raltegravir was administered in combination with an optimized background ART regimen.[11,16] Subjects received either the raltegravir 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 raltegravir 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 I: 12 years to <19 years; Cohort II: 6 years to <12 years, Cohort III: 2 years to <6 years). Doses were selected with the aim of achieving target PK parameters similar to those seen in adults: PK targets were a geometric mean (GM) AUC$_{0-12h}$ of 14 µM*hr to 25 µM*hr 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 raltegravir.

A total of 126 treatment-experienced participants were enrolled, with 96 participants receiving the final recommended dose of raltegravir. 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 CDC Category B or C classification. 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) cell count increase of 156 cells/mm^3 (4.6%).[11] Of 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 raltegravir-associated mutations were detected in 12 out of 34 of those patients. The frequency, type, and severity of adverse events (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. AEs that were considered to be drug-related included one patient with Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; and 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, raltegravir was well tolerated when it was 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]

Among 19 children and adolescents who were non-responders with multidrug-resistant virus in the HIV Spanish Cohort (CoRISe), all had good virologic response and improved CD4 counts when raltegravir was

included in an optimized regimen.[9] Experience from the French expanded access program in treatment-experienced adolescents supports the good virologic and immunologic results observed in IMPAACT P1066.[18,19] Overall virologic and immunologic outcomes have been good among additional cohorts of treatment-experienced children and adolescents from low-income and middle-income countries.[20,21]

Children Aged at Least 4 Weeks to <2 Years

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the granules for raltegravir oral suspension in combination with an optimized background 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 Cohorts IV and V were modified to a GM AUC_{0-12h} of 14 μM*hr to 45 μM*hr and a GM C_{12h} ≥75 nM (33.3 ng/mL). These targets were modified so that >90% of patients would be predicted to have C_{12h} above the 45 nM threshold. By Week 48, two subjects experienced AEs thought to be related to the study drug: one patient with a serious erythematous rash that resulted in permanent discontinuation of raltegravir, and one patient with 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 cell count increases of 527.6 cells/mm³ (7.3%). There were four subjects in Cohort IV who experienced virologic failure by Week 48 and one subject with a raltegravir-associated resistance mutation. Overall, the granules for oral suspension, at a dose of approximately 6 mg/kg twice daily, were well tolerated and had good efficacy.[10]

Long-Term Follow Up in Children

The IMPAACT P1066 study team recently reported results regarding the safety and efficacy of different raltegravir formulations at 240 weeks in children enrolled in this multicenter trial.[22] 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. Raltegravir was added to an optimized ART regimen in all participants. Raltegravir was well tolerated, and there were few serious clinical or laboratory safety events noted during the study.[22]

The proportion of participants who achieved virologic success at 240 weeks varied by the raltegravir formulation used: 19 of 43 children (44.2%) who received raltegravir 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. Raltegravir 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, while older children with an extensive treatment history are more likely to experience treatment failure and develop resistance to raltegravir. Poor adherence among adolescents may have contributed to the lower efficacy observed in older children who received the raltegravir 400-mg tablets.[22] In the accompanying commentary, the authors conclude that these findings support the use of raltegravir in infants and young children, who have few treatment options.[23] However, in older children and adolescents, INSTIs such as dolutegravir (which has a higher genetic barrier to resistance than raltegravir) would be preferred.[23]

Neonates Aged <4 Weeks

Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for UGT and albumin binding sites.[24] Washout PKs of raltegravir in neonates born to pregnant women with HIV was studied in IMPAACT P1097.[25] The neonatal plasma half-life was highly variable, ranging from 9.3 hours to 184 hours, suggesting potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of raltegravir.

IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates with or without *in utero*

raltegravir exposure who were exposed to HIV and who are at risk of acquiring HIV. Raltegravir-exposed neonates were those whose mothers received raltegravir within 2 hours to 24 hours of delivery. For raltegravir-exposed neonates, the initial dose of raltegravir was delayed until 12 hours to 60 hours after delivery. The study design included two cohorts: Cohort 1 infants received two raltegravir doses administered 1 week apart and Cohort 2 infants received daily raltegravir dosing 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 raltegravir dosing regimen for evaluation in infants in Cohort 2: 1.5 mg/kg daily, starting within 48 hours of life through Day 7; 3 mg/kg twice daily on Days 8 to 28 of life; 6 mg/kg twice daily after 4 weeks of age.[26,27] 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_{12hr} or C_{24hr} >33 ng/mL. Safety was assessed based on clinical and laboratory evaluations.[25,28,29] Twenty-six raltegravir-naive infants and 10 raltegravir-exposed infants were enrolled in Cohort 2; 25 raltegravir-naive infants and 10 raltegravir-exposed infants had evaluable PK results and safety data. Results for the raltegravir-naive infants and raltegravir-exposed infants who were enrolled in Cohort 2 are contained in the summary table below.

Table C. Raltegravir Pharmacokinetic Parameters for Raltegravir-Naive and Raltegravir-Exposed Neonates[29,30]

PK Parameter	After Initial Dose: 1.5 mg/kg Once Daily RAL-Naive (N = 25)		After Initial Dose: 1.5 mg/kg Once Daily RAL-Exposed (N = 10)		Days 15–18: 3.0 mg/kg Twice Daily RAL-Naive (N = 24)		Days 15–18: 3.0 mg/kg Twice Daily RAL-Exposed (N = 9)	
	Geometric Mean (CV%)	Target	Geometric Mean (CV%)	Target	Geometric Mean (CV%)	Target	Geometric Mean (CV%)	Target
AUC (mg*h/L)[a]	38.2 (38.4%)	Above: 11 Met: 13 Below: 0	42.9 (24.6%)	Above: 6 Met: 4 Below: 0	14.3 (43.3%)	Above: 8 Met: 14 Below: 1	18.3 (48.8%)	Above: 5 Met: 3 Below: 1
Trough (ng/mL)[b]	948 (64.2%)	Above: 25 Below: 0	946.3 (49.7%)	Above: 10 Below: 0	176 (93.8%)	Above: 22 Below: 1	273.6 (75.5%)	Above: 8 Below: 1
C_{max} (ng/mL)[c]	2,350 (35.0%)	Above: 0 Below: 25	2,565.3 (24.3%)	Above: 0 Below: 10	2,850 (41.9%)	Above: 0 Below: 24	3,667.4 (46.7%)	Above: 0 Below: 9
T_{max} (hours)	5.4 (57.5%)	N/A	3.8 (58.3%)	N/A	2.3 (67.1%)	N/A	1.9 (59.4%)	N/A
$T_{1/2}$ (hours)	15.8 (174.8%)	N/A	14.4 (58.3%)	N/A	2.5 (33.5%)	N/A	2.9 (20.1%)	N/A

[a] The PK targets were AUC_{24} 12–40 mg*h/L and AUC_{12} 6–20 mg*h/L.

[b] The trough concentration target was >33 ng/mL.

[c] The C_{max} target was <8,724 ng/mL.

Key to Acronyms: AUC = area under the curve; Cmax = maximum concentration; CV = coefficient of variation; PK = pharmacokinetic; RAL = raltegravir; $T_{1/2}$ = half-life; T_{max} = time to reach maximum concentration

Daily raltegravir 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_{0-24hr} following the initial dose was slightly above the target range, but this is considered acceptable given the rapid increase in raltegravir metabolism during the first week of life. The PK targets and the safety guidelines were met for both raltegravir-naive and raltegravir-exposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory adverse reactions were reported among the raltegravir-naive infants: Grade 4 transient neutropenia occurred in one infant receiving 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 raltegravir-exposed infants, there were four infants with 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 P1110 confirmed the PK modeling and simulation submitted for FDA approval and labeling. Neonates born to mothers who received raltegravir 2 hours to 24 hours prior to delivery should have their first dose of raltegravir delayed until 24 hours to 48 hours after birth.[30]

Dosing in preterm infants has not been well studied. Two case reports of preterm infants dosed with raltegravir to prevent perinatal transmission have been published.[31,32] 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 raltegravir was done using real-time therapeutic drug monitoring (TDM) in the neonatal intensive care unit.[31,32] Less frequent dosing was required because raltegravir elimination was significantly delayed in these preterm infants. A revised version of P1110 that will determine the PKs and safety of raltegravir in low birth weight neonates at risk of perinatal transmission of HIV is in development.

Formulations

The PKs of raltegravir in adult patients with HIV who swallowed intact 400-mg tablets were compared to 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.[33] In adult volunteers, the PKs of raltegravir 800 mg taken once daily by chewing was compared to the PKs of two doses of raltegravir 400 mg taken every 12 hours by swallowing. Participants who took raltegravir by chewing had significantly higher drug exposure and reduced PK variability than those who swallowed whole tablets as currently recommended.[34] According to the manufacturer, the film-coated tablets must be swallowed whole.

The raltegravir 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.[35] Compared with the raltegravir 400-mg tablet formulation, the raltegravir 600-mg tablet has higher relative bioavailability.[3,36] Interpatient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.[3,37] Because of differences in the bioavailability of various formulations, the dosing recommendations for each formulation differ, and the formulations **are not interchangeable**. When prescribing raltegravir, clinicians should refer to the appropriate dosing table for the chosen formulation. While the raltegravir chewable tablets are not yet approved for use in children aged <2 years, a recent study has investigated whether these tablets may be dispersed and administered to younger children and infants.[38] An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including breast milk. A follow-up evaluation of chewable tablets used as dispersible tablets for young children is planned.

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]

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Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

Cobicistat (COBI, Tybost)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Tablet: 150 mg

Fixed-Dose Combination Tablets:

- [*Evotaz*] Atazanavir 300 mg/cobicistat 150 mg
- [*Genvoya*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide (TAF) 10 mg
- [*Prezcobix*] Darunavir 800 mg/cobicistat 150 mg
- [*Stribild*] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
- [*Symtuza*] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/TAF 10 mg

Dosing Recommendations

Cobicistat is a Pharmacokinetic Enhancer:

- The only use of cobicistat is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase inhibitors. Cobicistat **is not interchangeable** with ritonavir.

Use of Cobicistat-Containing Drugs in Children and Adolescents

Not Food and Drug Administration (FDA)-Approved for Use in Children and Adolescents Aged <18 Years:

- Cobicistat alone (as Tybost)
- Evotaz
- Prezcobix
- Symtuza
- Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) regard the above agents as potentially appropriate for use in certain children aged <18 years and weighing ≥35 kg. An expert in pediatric HIV infection should be consulted before using these drugs in these patients. See the atazanavir and darunavir sections for additional information.

FDA-Approved for Use in Children and Adolescents Weighing ≥25 kg:

- Genvoya

FDA-Approved for Use in Children and Adolescents Aged ≥12 and Weighing ≥35 kg:

- Stribild
- The Panel recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.

Selected Adverse Events

- Cobicistat 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

- Cobicistat 150 mg is **not interchangeable** with ritonavir, but it has a PK boosting effect that is comparable to ritonavir 100 mg.
- Drug interactions may differ between ritonavir and cobicistat, because cobicistat is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of ritonavir.
- Genvoya, Stribild, and Symtuza are approved for use in treatment-naive patients. They can also 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 for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of these single-tablet regimens.
- **Do not administer** cobicistat with ritonavir or with FDC tablets that contain cobicistat.
- Not recommended for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI).
- Use with PIs other than once-daily atazanavir 300 mg or darunavir 800 mg **is not recommended**.
- Patients with a confirmed increase in serum

Adult (Aged ≥18 Years) Dose

Cobicistat Must be Administered as:

- The fixed-dose combination (FDC) tablets Stribild, Genvoya, or Symtuza, which are complete regimens and should not be administered with any other antiretroviral (ARV) drugs; *or*

- The tablet Tybost, which should be administered at the same time as atazanavir or darunavir at the doses listed in the table below and used in combination with other ARV drugs; *or*

- The FDC tablets Evotaz (which also contains atazanavir) or Prezcobix (which also contains darunavir). Both FDC tablets should be administered with food and in combination with other ARV drugs.

Doses for Cobicistat and Coadministered Antiretroviral Drugs

Cobicistat Dose	Coadministered Agent Dose	Patient Population
150 mg orally once daily	As part of Stribild, Genvoya, or Symtuza	Treatment-naive or treatment-experienced, with virus that is susceptible to all ARV drug components of Stribild, Genvoya, or Symtuza
150 mg orally once daily	Atazanavir 300 mg (coformulated as Evotaz or given as a separate drug) given orally once daily	Treatment-naive or treatment-experienced
150 mg orally once daily	Darunavir 800 mg (coformulated as Prezcobix or given as a separate drug) given orally once daily	Treatment-naive or treatment-experienced, with no darunavir-associated resistance mutations

creatinine >0.4 mg/dL from baseline should be closely monitored for renal safety.

- When using cobicistat in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 months to 6 months while the patient is receiving therapy (see Table 15i). In patients who are at risk of renal impairment, serum phosphate should also be monitored.

- When using cobicistat in combination with other ARV drugs, or when using FDC tablets that contain cobicistat, see other drug sections for special instructions and additional information about the individual drug components (e.g., atazanavir, darunavir, elvitegravir, TDF, TAF).

Metabolism/Elimination

- Cobicistat is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.

Cobicistat Dosing in Patients with Renal Impairment:

- Stribild should not be initiated in patients with estimated creatinine clearance (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.

- Neither Genvoya nor Symtuza should be initiated in patients with estimated CrCl <30 mL/min.

- Stribild, Genvoya, and Symtuza should not be used in patients with severe hepatic impairment.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- *Metabolism:* Metabolism of cobicistat is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. Cobicistat is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. Cobicistat also inhibits the breast cancer resistance protein, P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1. Unlike ritonavir, cobicistat does not demonstrate any enzyme-inducing effects. The potential exists for multiple drug interactions when using cobicistat. Before cobicistat is administered, a patient's medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs.

- *Nucleoside reverse transcriptase inhibitors:* Cobicistat is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with cobicistat produces tenofovir exposures that are similar to those produced by TAF 25 mg without cobicistat.[1]

- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine **should not be used** with cobicistat.

- *Protease inhibitors:* Using cobicistat as a dual booster for elvitegravir and darunavir has been studied in people with HIV and people without HIV, and the evidence is conflicting. When elvitegravir plus cobicistat plus darunavir was administered to people without HIV, the C_{trough} concentration of elvitegravir was 50% lower than the C_{trough} concentration seen in people who received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (TDF) without darunavir.[2] When elvitegravir/cobicistat/emtricitabine/TAF was administered with darunavir to patients with HIV, both darunavir and elvitegravir concentrations were comparable to historic controls.[3]

- *Integrase inhibitors:* In one small study, dolutegravir C_{trough} concentrations were higher when dolutegravir was administered with darunavir/cobicistat (DRV/c) than when it was administered with darunavir/ritonavir.[4] Bictegravir area under the curve increases 74% when bictegravir is administered with DRV/c.[5] Increased serum concentrations of corticosteroids can occur when corticosteroids and cobicistat 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) 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.[6]

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. Cobicistat has no antiviral activity. Its sole use is as a pharmacokinetic enhancer of antiretroviral drugs.

Pediatric Use

Approval

The Food and Drug Administration (FDA) has not approved the use of cobicistat alone (as Tybost), cobicistat coformulated with atazanavir (as Evotaz) or darunavir (as Prezcobix), or cobicistat as a component of Symtuza in children aged <18 years. Cobicistat, as a component of Stribild, is approved by the 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 use to those with a sexual maturity rating of 4 or 5. Cobicistat, as a component of Genvoya, is approved by the FDA at the adult dose for use in children weighing ≥25 kg.

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Ritonavir (RTV, Norvir) <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

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

<mark>**Generic Formulation**</mark>

<mark>**Tablets:** 100 mg</mark>

Fixed-Dose Combination Solution:

- <mark>[*Kaletra*] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol.</mark>

Fixed-Dose Combination Tablets:

- <mark>[*Kaletra*] Lopinavir 100 mg/ritonavir 25 mg</mark>
- <mark>[*Kaletra*] Lopinavir 200 mg/ritonavir 50 mg</mark>

Dosing Recommendations

Ritonavir as a Pharmacokinetic Enhancer:[a]

- Ritonavir is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See other sections of the Drug Appendix for information about the recommended doses of ritonavir to use with specific PIs.

Formulation Considerations:

- The 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 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- Ritonavir oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

[*Kaletra*] Lopinavir/Ritonavir

Infant, Child, Adolescent, and Adult Dose:

- See the <mark>Lopinavir/Ritonavir</mark> section of the <mark>Drug Appendix</mark>.

Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Hyperglycemia
- Fat maldistribution

Special Instructions

- Administer ritonavir with food to increase absorption and reduce the likelihood and severity of GI adverse events.
- **Do not administer** ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild, Genvoya, Prezcobix, Evotaz).
- **Do not refrigerate** ritonavir oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- Ritonavir oral powder should be mixed with a soft food (e.g., apple sauce, 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 in Children:

- Mix the solution with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.
- Before administering ritonavir, 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 child peanut butter to coat the mouth.
- After administration, give strong-tasting foods (e.g., maple syrup, cheese).
- Check a child's food allergy history before making these recommendations.
- Counsel parents 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. Ritonavir inhibits the intestinal transporter P glycoprotein.

Ritonavir Dosing in Patients with Hepatic Impairment:

- Ritonavir is primarily metabolized by the liver. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. There are no data on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.

[a] Ritonavir has antiviral activity, but it is not used as an antiviral agent (see text).

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- *Metabolism:* Ritonavir is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P450 (CYP) 3A. Also, ritonavir is a CYP2D6 inhibitor and a CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. Ritonavir inhibits the intestinal transporter P glycoprotein. There is potential for multiple drug interactions with ritonavir.

- Before ritonavir is administered, a patient's medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.

- Ritonavir and cobicistat **are not interchangeable**. The potential drug interactions for these drugs are different.[1]

- Avoid concomitant use of intranasal or inhaled fluticasone. Reduced elimination of steroids can increase steroid effects, leading to adrenal insufficiency.[2] Use caution when prescribing ritonavir with other

inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking ritonavir requires an inhaled or intranasal corticosteroid.[3,4] In one case, a patient developed iatrogenic Cushing syndrome and suppression of the hypothalamic-pituitary axis secondary to the drug interaction between ritonavir and intra-articular triamcinolone injection.[5] 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, lipid abnormalities.

- *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, and 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.[6]

Resistance

Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

Pediatric Use

Approval

Ritonavir has been approved by the Food and Drug Administration for use in the pediatric population.

Effectiveness in Practice

Use of ritonavir as the sole protease inhibitor (PI) in ARV therapy in children **is not recommended**. In both children and adults, ritonavir is recommended as a PK enhancer for use with other PIs. Ritonavir is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PIs.

Dosing

Pediatric dosing regimens, including boosted darunavir, atazanavir, and the PI coformulation lopinavir/ritonavir (LPV/r), are available. For more information about individual PIs, see other sections of the [Drug Appendix](...).

Toxicity

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir 400 mg twice daily.[6] Potentially life-threatening arrhythmias have been reported in premature newborn infants who were treated with LPV/r; the use of LPV/r **is not recommended** before a gestational age of 42 weeks.[7,8] Coadministration of ritonavir 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 ritonavir will affect the PR interval. In addition, ritonavir 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

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents

Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

Brand Name by Class	NRTIs						NNRTIs			INSTIs			PIs			PK Enhancers	
	ABC	3TC	ZDV	FTC	TDF	TAF[a]	DOR	EFV	RPV	BIC[a]	DTG	EVG[a]	ATV	DRV	LPV[b]	COBI	RTV
NRTI																	
Cimduo		X			X												
Combivir, Generic		X	X														
Descovy				X		X											
Epzicom, Generic	X	X															
Temixys		X			X												
Trizivir, Generic	X	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							
Triumeq	X	X									X						
NNRTI/INSTI																	
Juluca									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

Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

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 LPV is only available in fixed-dose tablets or solution.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; LPV = lopinavir; LPV/r = 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: Minimum Body Weights and Considerations for Use in Children and Adolescents (page 1 of 3)

This table may include recently approved FDCs that have not yet been added to individual drug sections in the Pediatric Antiretroviral Drug Information Appendix (see individual drug components for details).

General Considerations When Considering an FDC Tablet:

- ABC and TAF are favored over ZDV because of lower risk of NRTI-associated mitochondrial toxicity.

- 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 generally **not recommended** for children with SMR 1–3 because of TDF-associated bone toxicity; however, for a child weighing <25 kg who can swallow pills, Truvada (FTC/TDF) low-strength tablets offer a reasonable, once daily combination alternative to twice daily ZDV plus 3TC or an alternative to ABC.

- 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.

- BIC and DTG, second-generation INSTIs, have a higher barrier to resistance than EVG and RAL, first-generation INSTIs.

- For images of most of the FDCs 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 FDCs and individual ARVs (see the Intro 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 Appendix A, Table 2 below.

- FDCs and individual ARVs can also be looked up by drug (brand name and generic) at DailyMed; size is listed under Ingredients and Appearance in the Product Characteristics section.

- INSTI FDC Dosing for Children and Adolescents:

- Elvitegravir:

  - Genvoya (EVG/COBI/FTC/TAF) is FDA approved for children and adolescents weighing ≥25 kg.

- Dolutegravir:

  - The Panel recommends DTG 50 mg for children weighing ≥25 kg, see the dolutegravir section. The FDA-approved dose is DTG 35 mg for patients weighing ≥30 kg to 40 kg, and DTG 50 mg for patients weighing ≥40 kg.

  - DTG 50 mg can be given as Triumeq (ABC/DTG/3TC) in 1 large pill or as Descovy (FTC/TAF) plus DTG which requires 2 small pills.

  - Recent data identified a possible increased risk of NTDs among women who were receiving DTG at the time of conception. Specific recommendations about the initiation and use of DTG in adolescents and women of childbearing potential and in pregnant women are available in the Adult and Adolescent Antiretroviral Guidelines (See Table 6b and Adolescents and Young Adults with HIV) and in the Perinatal Guidelines (see Teratogenicity and Recommendations for the Use of Antiretroviral Drugs in Pregnancy).

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (page 2 of 3)

- Bictegravir:
  - Biktarvy (BIC/FTC/TAF) has been studied in children and adolescents aged ≥6 years and weighing ≥25 kg but is not FDA approved for use in patients aged <18 years.

FDC by Class Brand name and generic[a] products, when available	FDC Components	Minimum Body Weight (kg) or Age[b]	Pill Size (mm x 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 x 7	Take with or without food
Descovy	FTC 200 mg/TAF 25 mg	25 kg: With INSTI or NNRTI 35 kg: With boosted PI	12.5 x 6.4	Take with or without food
Epzicom and Generic ABC/3TC	ABC 600 mg/3TC 300 mg	25 kg	21 x 9	Take with or without food
Temixys	3TC 300 mg/TDF 300 mg	35 kg	N/A	Take with or without food
Trizivir and Generic ABC/3TC/ZDV	ABC 300 mg/3TC 150 mg/ZDV 300 mg	40 kg 30 kg (Panel)[c]	21 x 10	Take with or without food
Truvada	FTC 200 mg/TDF 300 mg	35 kg	19 x 8.5	Take with or without food
Truvada Low Strength	FTC 167 mg/TDF 250 mg	28 kg	18	Take with or without food
	FTC 133 mg/TDF 200 mg	22 kg	16	Take with or without food
	FTC 100 mg/TDF 150 mg	17 kg	14	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
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	Adults	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[d]	21	Take on an empty stomach
NRTI/INSTI				
Biktarvy	BIC 50 mg/FTC 200 mg/TAF 25 mg	Adults	15 x 8	Take with or without food

Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (page 3 of 3)

FDC by Class Brand name and generic[a] products, when available	FDC Components	Minimum Body Weight (kg) or Age	Pill Size (mm x mm) or Largest Dimension (mm)	Food Requirements
NRTI/INSTI, continued				
Triumeq	ABC 600 mg/DTG 50 mg/3TC 300 mg	40 kg 25 kg (Panel)[e]	22 x 11	Take with or without food
NNRTI/INSTI				
Juluca	DTG 50 mg/RPV 25 mg	Adults	14	Take with a meal
NRTI/INSTI/COBI				
Genvoya	EVG 150 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	25 kg	19 x 8.5	Take with food
Stribild	EVG 150 mg/COBI 150 mg/FTC 200 mg/TDF 300 mg	35 kg	20	Take with food
NRTI/PI/COBI				
Symtuza	DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	Adults	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	35 kg	23	Take with food
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] Size or largest dimension 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] Based on the current FDA-approved minimum body weights for Trizivir component drugs, the Panel suggests Trizivir may be used at a minimum body weight of ≥30 kg, although it is FDA approved for use in children and adolescents ≥40 kg. However, the Panel does not recommend regimens containing NRTI's only, or 3-NRTI regimens, for use in children.

[d] Due to pharmacokinetic concerns, the Panel recommends caution when using Symfi Lo in children and adolescents who have a SMR 1-3 and weigh ≥40 kg, see the efavirenz section.

[e] The Panel recommends using DTG 50 mg for children and adolescents weighing ≥25 kg based on available data, see the dolutegravir section.

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; DOR = doravirine; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; mm = millimetre; N/A = information not available; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside and nucleotide reverse transcriptase 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 (ddl, 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/m^2 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/m^2 body surface area every 12 hours

Pediatric Dose of Oral Solution (Age >8 Months):
- 120 mg/m^2 body surface area every 12 hours
- Dose range: 90–150 mg/m^2 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/m^2 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/m² of body surface area twice daily.[3,4] Doses higher than 180 mg/m² 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/m² 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/m² of body surface area twice daily for infants aged 2 weeks to 3 months, with an increase to 100 mg/m² of body surface area per dose twice daily at 3 months, and finally increasing to 120 mg/m² 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/m² 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 Ritonavir

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_{0-24h} (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_{0-12} (mcg*hr/mL)

Key to Acronyms: AUC_{0-24h} = 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 (59–86ºF) 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 <mark>(Last updated April 16, 2019; last reviewed April 16, 2019)</mark>

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
BIC	bictegravir
COBI or /c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IBA	ibalizumab
IDV	indinavir
LPV	lopinavir
MVC	maraviroc
NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or /r	ritonavir
SQV	saquinavir
T20 or T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	zidovudine

Drug Name Abbreviations

Acronym	Term
° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse effect
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APHL	Association of Public Health Laboratories
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-12h}	area under the curve at 12 hours post-dose
AUC_{24h}	area under the curve at 24 hours post-dose
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_{12} or C_{12h}	mid-dose concentration
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
CV	coefficients of variation
CVD	cardiovascular disease
CYP	cytochrome P
dL	deciliter
DM	diabetes mellitus
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DOT	directly observed therapy
DRESS	drug reaction (or rash) with eosinophilia and systemic symptoms

Acronym	Term
DSMB	Data Safety Monitoring Board
DXA	dual energy x-ray absorptiometry
EBV	Epstein-Barr virus
EC	enteric-coated
ECG or EKG	electrocardiogram
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EM	erythema multiforme or extensive metabolizers
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDC	fixed-dose combination
fL	femtoliter
fmol	femtomole
FLP	fasting lipid profile
FPG	fasting plasma glucose
G6PD	glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
GI	gastrointestinal
GM	geometric mean
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
HgbA1c	glycosylated hemoglobin
HHS	Department of Health and Human Services
HIV RNA or HIV-1 RNA	viral load
HLA	human leukocyte antigen
HPV	human papilloma virus
HRSA	Health Resources and Services Administration
HSR	hypersensitivity reaction
HSV	herpes simplex virus
IAS-USA	International Antiviral Society-USA
ICH	intracranial hemorrhage
INH	isoniazid
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IQR	interquartile range
IRIS	immune reconstitution inflammatory syndrome
IU	international units
IV	intravenous
IVIG	intravenous immune globulin

Acronym	Term
kg	kilogram
L	liter
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LLD	lower level of detection
LLQ	lower limits of quantitation
LS	lipodystrophy syndrome
mcg or μg	microgram
MCV	mean cell volume
mg	milligram
min	minute
mL	milliliter
mm	millimeter
NASBA	nucleic acid sequence-based amplification
NAT	nucleic acid test
ng	nanogram
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
OBT	optimized background therapy
OGTT	oral glucose tolerance test
OI	opportunistic infection
oz	ounce
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
py	patient years
QTc	corrected QT
RBV	ribavirin
RNA	ribonucleic acid
RPG	random plasma glucose
RT-PCR	reverse transcription polymerase chain reaction

Acronym	Term
SCT	short-cycle therapy
SD	standard deviation
SDD	study drug discontinuation
SJS	Stevens-Johnson syndrome
SM	slow metabolizers
SMR	sexual maturity rating
SQ	subcutaneous
STI	sexually transmitted infection
$T_{1/2}$	half-life
TB	tuberculosis
TC	total cholesterol
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrolysis
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TG	triglyceride
THAM	tris (hydroxymethyl) aminomethane
T_{max}	time to reach maximum concentration
TMP-SMX	trimethoprim sulfamethoxazole
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
VLS	viral load suppression
WHO	World Health Organization

Appendix C: Supplemental Information (Last updated February 12, 2014; last reviewed February 12, 2014)

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 and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)

	Absolute CD4 Cell Count (cells/mm^3)					
Age (Years)	<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 CD4 T-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 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
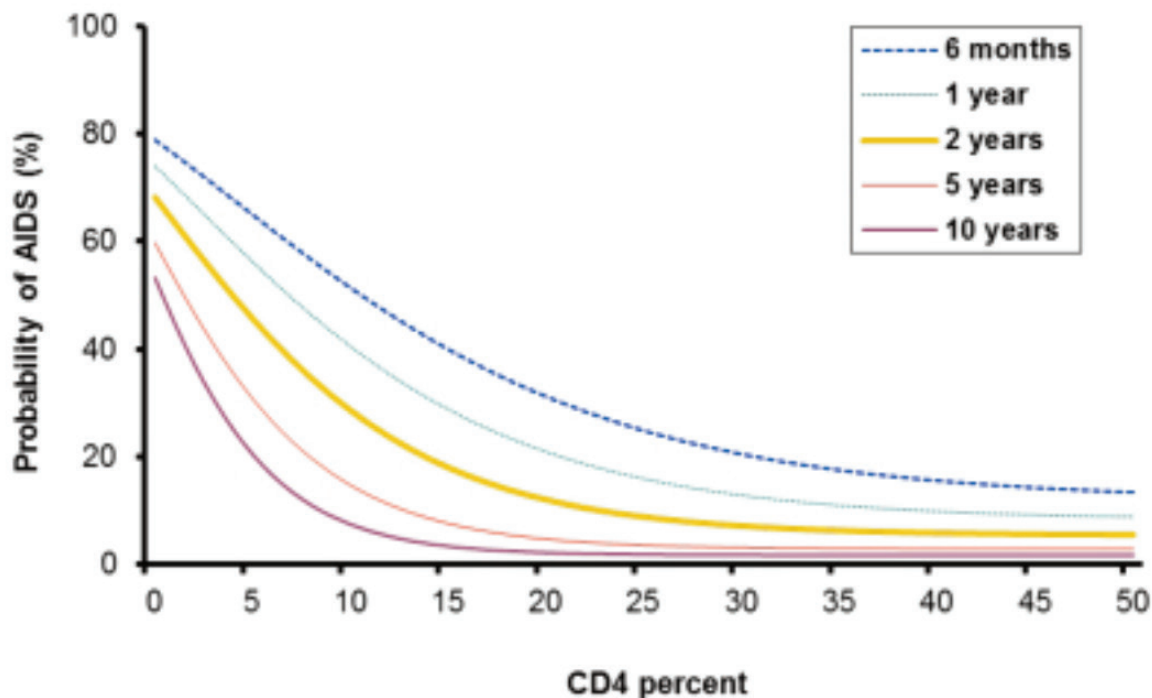

Figure modified from *Lancet* 2003;362:1605-1611

Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy
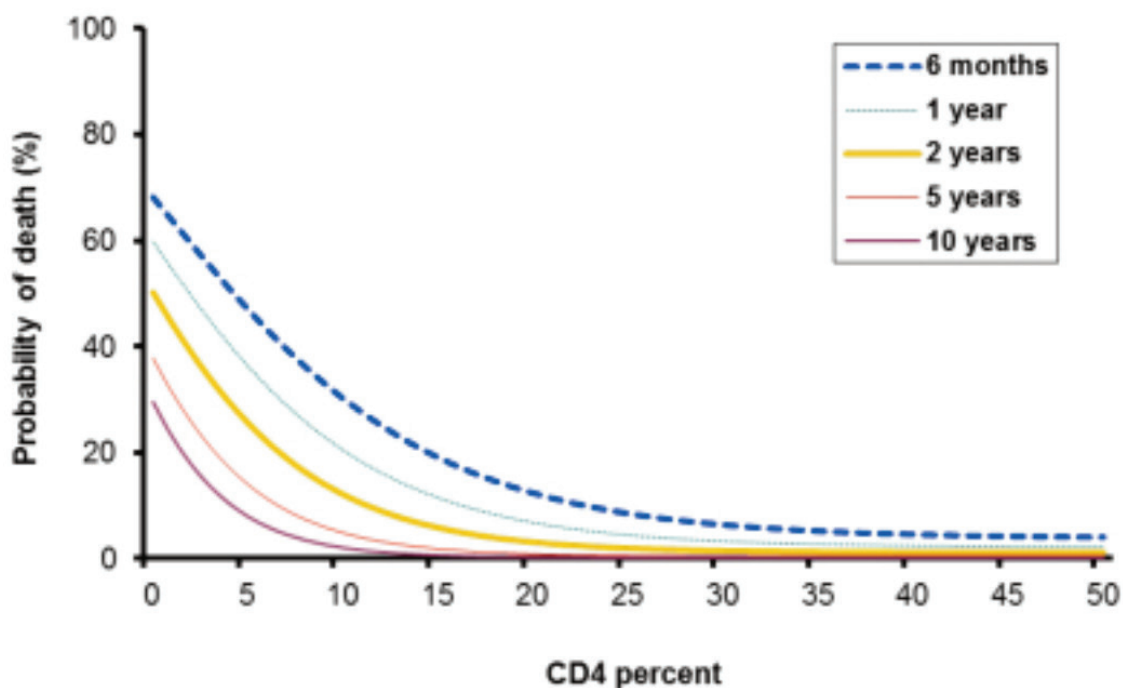

Figure modified from *Lancet* 2003;362:1605-1611

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*
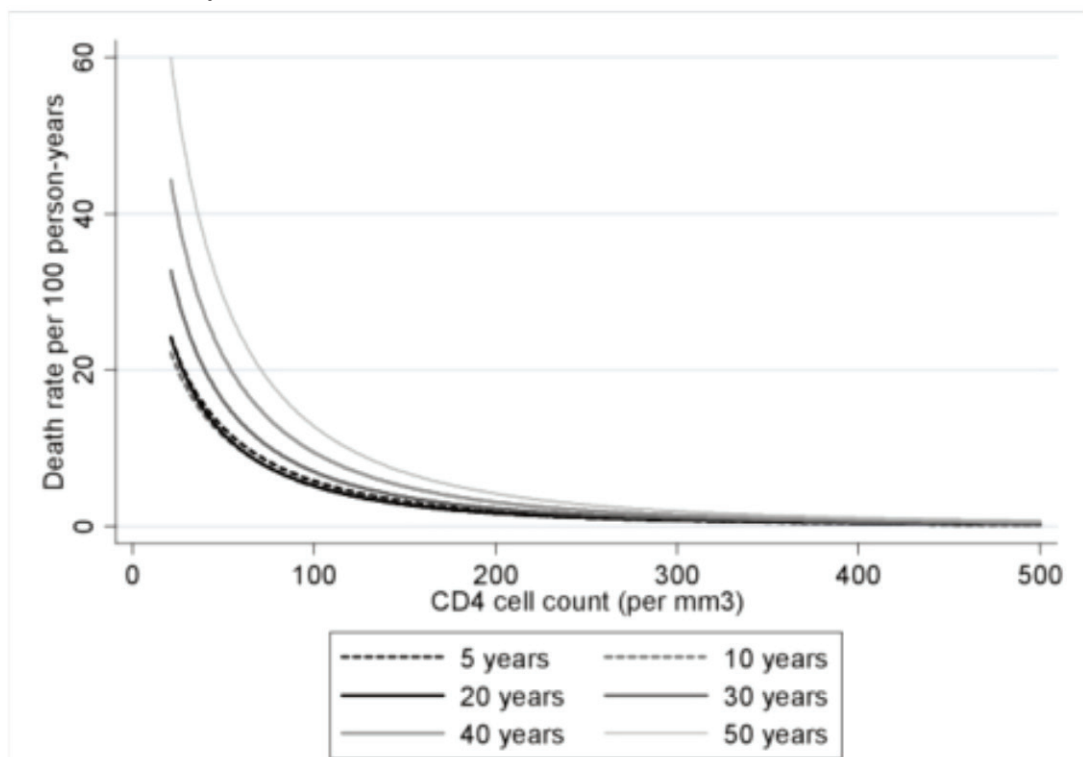

Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis.* 2008;197:398-404.

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
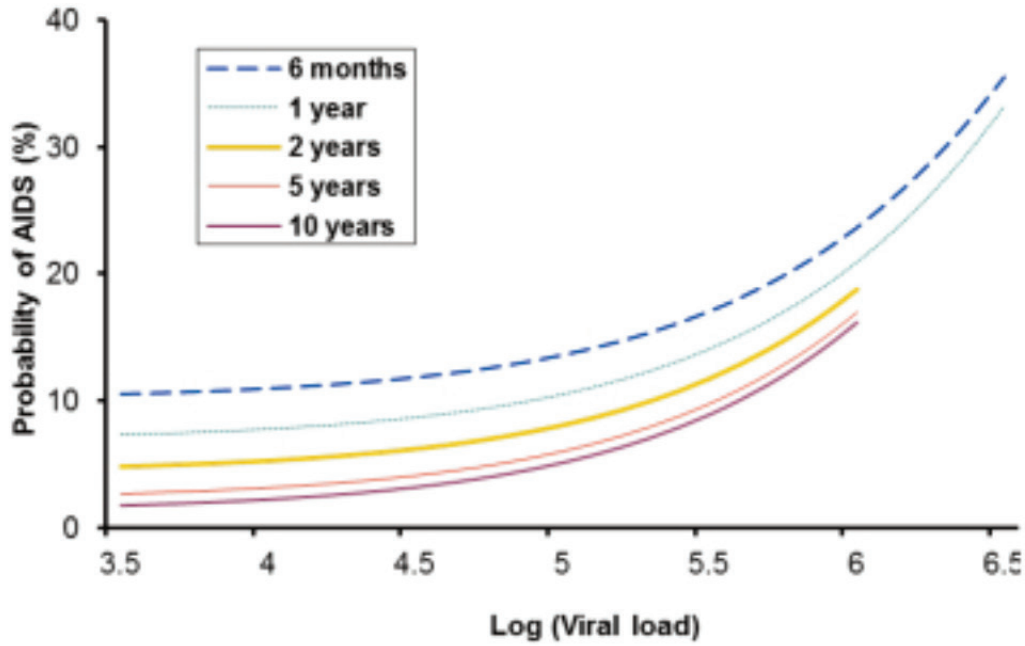

Figure modified from *Lancet* 2003;362:1605-1611

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
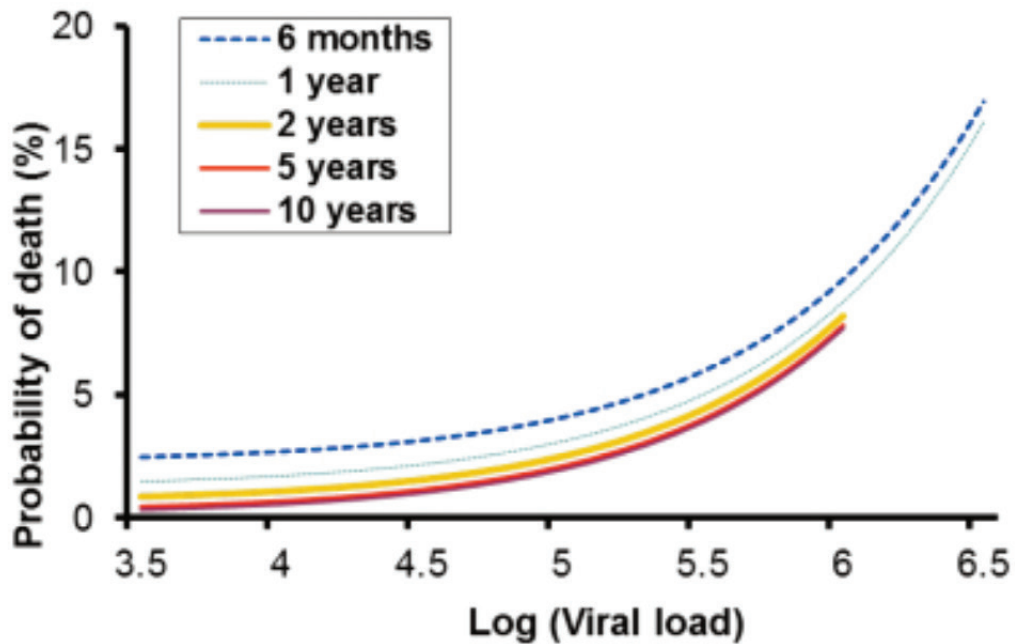

Figure modified from *Lancet* 2003;362:1605-1611