



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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# 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:

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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 (Last updated April 14, 2020; last reviewed April 14, 2020)

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

### April 14, 2020

#### *When to Initiate Therapy in Antiretroviral-Naive Children*

- The Panel now recommends rapid initiation of antiretroviral therapy (ART) for **all** children, not just those aged <1 year. Rapid initiation is defined as initiating therapy immediately or within days of HIV diagnosis.
- Because the Panel no longer makes recommendations about when to initiate ART based on a child's age (either <1 year of age or ≥1 year of age), Table A has been deleted and the data that support rapid initiation have been grouped by outcome (i.e., survival and health benefits, neurodevelopmental benefits, immune benefits, and viral reservoirs and viral suppression). References have been updated to reflect recently published findings, and older references have been removed.
- The Panel acknowledges that, on a case-by-case basis, initiation of ART may be deferred based on a patient's clinical or psychosocial factors. The Panel highlights medical factors, including HIV signs and symptoms, that should be considered when clinicians, patients, and caregivers make collaborative decisions about whether to defer treatment.
- With the changes described above, the Treatment Recommendations section is no longer needed and has been deleted.

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

- Text and Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children have been updated following Food and Drug Administration (FDA) approval of cobicistat (COBI) for pediatric use.
- The Panel now recommends atazanavir (ATV) boosted with COBI (ATV/c) or darunavir (DRV) boosted with COBI (DRV/c) plus two nucleoside reverse transcriptase inhibitors as *Alternative* protease inhibitor-based initial regimens for children and adolescents aged ≥12 years with a sexual maturity rating of 1 to 3 who weigh ≥35 kg or ≥40 kg, respectively.
- Throughout the guidelines, the Panel refers to the Adult and Adolescent Antiretroviral Guidelines and the Perinatal Guidelines for guidance about the use of dolutegravir (DTG) and other antiretroviral (ARV) drugs in people of childbearing potential and those who are pregnant or who are trying to conceive.
  - Wording has been revised in accordance with updated recommendations about the use of DTG, and a link to the new [Appendix D. Dolutegravir Counseling Guide for Health Care Providers](#) in the Perinatal Guidelines has been inserted into several sections.

#### *Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection*

- The Panel has changed the term “empiric HIV therapy” to “presumptive HIV therapy” in this section and throughout the guidelines to be consistent with the terminology used by the World Health Organization. The Panel recommends presumptive HIV therapy for infants who are at a higher risk of perinatal HIV

acquisition. For clarity, the term “multidrug ARV prophylaxis” has been changed to “two-drug ARV prophylaxis.”

- Table 11. Neonatal Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 12. Antiretroviral Dosing Recommendations for Newborns have been revised to clarify the ARV regimens and the duration and dosing of ARV drugs that are used for presumptive HIV therapy.
- The two-drug regimen that was used in NICHD-HPTN 040/PACTG 1043 for infants who were at a higher risk of HIV acquisition is no longer included in Tables 11 and 12; this regimen is described in the text instead, see the [Two-Drug Antiretroviral Prophylaxis](#) section.

### **Special Considerations for Antiretroviral Therapy Use in Adolescents with HIV**

- The Panel added a new subsection entitled Special Considerations for Adolescents with HIV Who Are Sexual Minorities with links to [Adolescents and Young Adults with HIV](#) and [Transgender People with HIV](#) in the Adult and Adolescent Antiretroviral Guidelines.

### **Management of Medication Toxicity or Intolerance**

- [Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity](#) includes updated information about neuropsychiatric symptoms and other central nervous system manifestations that are associated with the use of integrase strand transfer inhibitors. Information on bictegravir has also been added to the table.
- Information about the association between ARV drugs and weight gain has been added to [Table 15h](#), and the table has been renamed Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain.

### **Management of Children Receiving Antiretroviral Therapy**

- The sections on [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#) and [Recognizing and Managing Antiretroviral Treatment Failure](#) have been updated to incorporate the most recent ART options for pediatric patients based on new pediatric ARV drug approvals and Panel recommendations.

### **Appendix A: Pediatric Antiretroviral Drug Information**

The drug sections and [Appendix A, Table 2](#) were updated to include new pediatric data and dosing and safety information, plus new drug formulations and fixed-dose combination (FDC) drugs. Significant changes include:

- In accordance with FDA approval, raltegravir (RAL) HD is now recommended for use in children and adolescents weighing  $\geq 40$  kg who are treatment naive or who are virologically suppressed on an initial dose of RAL 400 mg twice daily.
- Although lopinavir/ritonavir is not approved by the FDA for use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days, the Panel now provides some guidance for situations where no alternatives are available for neonates who have not met these age thresholds.
- The ATV, DRV, and COBI drug sections have been updated to reflect recent FDA approvals and updated Panel recommendations. COBI (Tybost) is now approved by the FDA for use with ATV in children and adolescents weighing  $\geq 35$  kg and for use with DRV in children and adolescents weighing  $\geq 40$  kg. The FDC tablet darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/c/FTC/TAF; Symtuza) is now approved by the FDA for use in children and adolescents weighing  $\geq 40$  kg. Although coformulated ATV/c (Evotaz) and DRV/c (Prezcobix) are not approved by the FDA for use in children, the Panel does recommend using these FDC tablets in pediatric patients weighing  $\geq 35$  kg or  $\geq 40$  kg, respectively, based on FDA approvals of the individual component drugs.

## December 24, 2019

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has updated the three sections of the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* that developed in collaboration with the Panel on Treatment of Pregnant Women.

### [Maternal HIV Testing and Identification of Perinatal HIV Exposure](#)

In addition to recommendations for repeat HIV testing in the third trimester, repeat HIV testing at other times during pregnancy should be considered when clinically indicated. For example, repeat testing should be performed when a woman presents with symptoms that are suggestive of a sexually transmitted infection (STI), when a woman presents with a confirmed STI diagnosis, or when a woman presents with symptoms that are consistent with acute HIV infection.

### [Diagnosis of HIV Infection in Infants and Children](#)

The Panel has added some guidance about when consultation with a clinical virologist may be indicated when the mother of an infant acquired HIV infection outside of the U.S. and has had repeated undetectable HIV RNA by standard testing.

### [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#)

When considering the risk of perinatal HIV transmission and the selection of appropriate ARV drugs for newborns with perinatal HIV exposure, the Panel now defines maternal viral suppression as an HIV RNA level of <50 copies/mL.

A new subsection summarizes information about choosing between empiric HIV therapy and multidrug ARV prophylaxis for newborns with perinatal HIV exposure who are at a high risk of perinatal HIV transmission.

The Panel has also clarified that nevirapine (NVP) can be replaced with lopinavir/ritonavir when infants who are receiving empiric HIV therapy reach a postmenstrual age  $\geq 42$  weeks and a postnatal age  $\geq 14$  days; NVP can be replaced with RAL at any age.

## September 12, 2019

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) revised several sections of the April 16, 2019 *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* to update content and recommendations about the use of the antiretroviral drugs bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) and dolutegravir in children and adolescents. The updates are summarized below.

### [What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children](#)

- Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, Figure 1, and the associated text now include new recommendations for the use of bictegravir and dolutegravir in children:
  - The fixed-dose combination (FDC) tablet Biktarvy is now a *Preferred* integrase strand transfer inhibitor (INSTI)-based regimen for adolescents aged  $\geq 12$  years and weighing  $\geq 25$  kg (**AI**) and an *Alternative* INSTI-based regimen for children aged  $\geq 6$  years and weighing  $\geq 25$  kg (**AI**).
  - Dolutegravir plus two nucleoside reverse transcriptase inhibitors is now an *Alternative* INSTI-based regimen for children aged  $\geq 3$  years and weighing  $\geq 20$  kg to  $< 25$  kg (**AI\***). It was previously recommended only for children weighing  $\geq 25$  kg. Data are limited on the efficacy and safety of

administering dolutegravir to children weighing  $\geq 20$  kg to  $< 25$  kg and dolutegravir pharmacokinetics vary more among children in this weight group than among those weighing  $\geq 25$  kg.

- Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children now includes information about Biktarvy.

### **What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children**

- Bictegravir was removed from this section following Food and Drug Administration (FDA) approval for the use of Biktarvy in children and adolescents weighing  $\geq 25$  kg.

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

- Table 16. Examples of Changes in Antiretroviral Regimen Components for Children with Sustained Virologic Suppression has been updated to reflect revised recommendations for the use of bictegravir and dolutegravir.

### **Appendix A: Pediatric Antiretroviral Drug Information**

- Certain drug sections and [Tables 1](#) and [2](#) were updated to include new pediatric data and dosing information for bictegravir and dolutegravir, including a new FDC tablet.
  - Bictegravir, which is available only in the FDC tablet Biktarvy, is now approved by the FDA for use in children and adolescents weighing  $\geq 25$  kg.
  - Based on recent data, the dosing recommendations for dolutegravir have been revised to allow use in children weighing  $\geq 20$  kg, although dolutegravir is not approved by the FDA for use in children weighing  $< 30$  kg. A new table in this section compares FDA, European Medicines Agency (EMA), World Health Organization (WHO), and Panel dosing recommendations for dolutegravir. Dolutegravir/lamivudine (Dovato), a new FDC tablet that has been approved for use in adults, was added to the Dolutegravir and Lamivudine sections and to Tables 1 and 2.
  - The Emtricitabine and Tenofovir Alafenamide sections have been updated to reflect changes in the dosing recommendations for FDC tablets that contain bictegravir or dolutegravir.

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## Members of Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (Last updated April 14, 2020; last reviewed April 14, 2020)

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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Purswani, Murli	M	None	N/A
Rakhmanina, Natella	M	<b>1. Merck</b> 2. Gilead	1. Research Support 2. Research Support
Raneri, Leslie	M	None	N/A
Ruel, Theodore D.	VC	None	N/A

## HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV Financial Disclosure (Last updated April 14, 2020; last reviewed April 14, 2020)

Name	Panel Status	Company	Relationship
Rutstein, Richard M.	M	None	N/A
Siberry, George K.	M	None	N/A
Storm, Deborah	NVO	1. Eli Lilly and Company 2. Merck 3. Roche	1. Stockholder 2. Stockholder 3. Stockholder and stock options
Weinberg, Geoffrey A.	M	Merck	Honoraria

**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 (Last updated April 14, 2020; last reviewed April 14, 2020)

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 \[SMRs 4–5\]](#)). 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 regularly updates the guidelines. The guidelines are available on the [AIDSinfo website](#).

The AIDSinfo website also provides separate guidelines for:

- The prevention and treatment of opportunistic infections (OIs) in children who were exposed to HIV and children with HIV infection;<sup>1</sup>
- The use of ARV drugs in adolescents and adults with HIV;<sup>2</sup>
- The use of ARV drugs in pregnant women with HIV;<sup>3</sup> and
- The prevention and treatment of OIs in adolescents and adults with HIV.<sup>4</sup>

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 HIV Infection](#)

Since the guidelines were first developed in 1993 (with the support of the François-Xavier Bagnoud Center, Rutgers, The State University of New Jersey), advances in medical management have dramatically reduced both the number of new pediatric HIV infections and the morbidity and mortality in children with HIV in the United States. The widespread use of ARV drugs in pregnant women 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 2016.<sup>5</sup> Since the introduction of ART, mortality in children with perinatal HIV infection has decreased by more than 80% to 90%, and the incidence of OIs and other infections in these children has significantly declined.<sup>6,7</sup> Children with HIV are less likely to develop AIDS because of routine and early initiation of effective ART.<sup>8–10</sup> ARV drug-resistance testing has made it easier for clinicians to choose effective initial and subsequent regimens. Treatment strategies focus on timely initiation of ARV regimens that are capable of maximally suppressing viral replication, which can prevent disease progression, preserve or restore immunologic function, and prevent the development of drug resistance. In addition, the availability of new drugs and drug formulations has led to more potent regimens with lower toxicity, lower pill burden, and less frequent medication administration—all factors that can improve adherence and outcomes. However, delays in the development and testing of pediatric formulations continue to limit the availability of optimal ARV regimens for children, especially infants.<sup>11</sup>

Children with HIV in the United States are increasingly foreign-born,<sup>12,13</sup> they may be members of immigrant families or they may have been adopted by U.S. residents. These children may have non-B subtypes of HIV, incomplete medical and treatment histories, an increased risk of tuberculosis and other infections that are endemic in their countries of origin, and legal and psychosocial needs related to immigration.

Finally, as children with HIV grow older, 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.<sup>14-17</sup>

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

- Acquisition of infection through perinatal exposure for most children with HIV;
- *In utero* and neonatal exposure to ARV drugs in most children with perinatal HIV infection;<sup>18</sup>
- The need to use HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months old;
- Age-specific interpretations of CD4 T lymphocyte (CD4) cell counts;
- Higher plasma viral loads in infants with perinatal HIV infection than in adolescents and adults with nonperinatal HIV infection;
- Age-related changes in PK parameters that are caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance;<sup>19</sup>
- Differences in the clinical manifestations and treatment of HIV in growing, immunologically immature individuals; *and*
- Special considerations associated with adherence to ARV treatment in infants, children, and adolescents.

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

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

**Table 1. Outline of the Guidelines Development Process**

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

**Table 1. Outline of the Guidelines Development Process, continued**

Topic	Comment
<b>Panel Members</b>	The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) is composed of approximately 34 voting members who have expertise in the management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection (e.g., parents and caregivers of children and youth with HIV). The Panel also includes at least one representative from each of the following Department of Health and Human Services (HHS) agencies: the Centers for Disease Control and Prevention (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 Paediatric and Perinatal HIV/AIDS Research Group participates as a nonvoting, <i>ex officio</i> 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 <a href="#">panel roster</a> .
<b>Financial Disclosure</b>	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 <a href="#">AIDSinfo website</a> .
<b>Users of the Guidelines</b>	Providers of care to infants, children, and adolescents with HIV in the United States
<b>Developer</b>	Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of the Office of AIDS Research Advisory Council (OARAC)
<b>Funding Source</b>	Office of AIDS Research, NIH, and HRSA
<b>Evidence Collection</b>	A standardized review of recent, relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel working groups. The recommendations 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.
<b>Recommendation Grading</b>	Described in <a href="#">Table 2</a>
<b>Method of Synthesizing Data</b>	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.
<b>Other Guidelines</b>	These guidelines focus on infants, children, and adolescents in early-to-mid-puberty (SMR 1–3) who are living with HIV. <a href="#">Guidelines for the treatment of adolescents in late puberty (SMR 4–5)</a> are provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents.  Separate guidelines outline the use of antiretroviral therapy (ART) in <a href="#">pregnant women with HIV</a> (including maternal and infant interventions to prevent perinatal transmission), ART for <a href="#">nonpregnant adults and postpubertal adolescents with HIV</a> , and ARV prophylaxis for those who experience <a href="#">occupational or nonoccupational exposure</a> to HIV. These guidelines are also available on the <a href="#">AIDSinfo website</a> .
<b>Update Plan</b>	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., <a href="#">What to Start</a> ). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the <a href="#">AIDSinfo website</a> 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.
<b>Public Comments</b>	A 2-week public comment period follows the release of the updated guidelines on the <a href="#">AIDSinfo website</a> . 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 <a href="mailto:contactus@aidinfo.nih.gov">contactus@aidinfo.nih.gov</a> .

## ***Basis for Recommendations***

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

When approving drugs for use in children, the Food and Drug Administration 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.<sup>20-22</sup>

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, the evidence from studies on the use of ARV drugs in adults (especially from randomized clinical trials) is much more substantial and higher in quality than the available evidence from studies in children. Therefore, for pediatric recommendations, the following rationale has been used when the evidence from studies in children is limited or of lower quality:

### **Quality of Evidence Rating I—Randomized Clinical Trial Data**

- Quality of Evidence Rating I will be used if there are data from large randomized trials **in children** with clinical and/or validated laboratory endpoints.
- Quality of Evidence Rating I\* will be used if there are high-quality randomized clinical trial data **in adults** with clinical and/or validated laboratory endpoints **and** pediatric data from well-designed, nonrandomized trials or observational cohort studies with clinical outcomes that are consistent with the adult studies. A rating of I\* may be used for quality of evidence if, for example, a randomized Phase 3 clinical trial in adults demonstrates that a drug is effective in ARV-naïve 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 treatment initiation at a similar CD4 cell count is associated with clinical benefit.

### **Quality of Evidence Rating III—Expert Opinion**

- The criteria do not differ for adults and children.

In an effort to improve the quality of evidence that is available to guide the management of HIV infection in children, clinicians are encouraged to discuss participation in trials with children and their caregivers. Information about clinical trials for adults and children with HIV can be obtained from the [AIDSinfo website](https://aidsinfo.nih.gov) or by telephone at 1-800-448-0440.

**Table 2. Rating Scheme for Recommendations**

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

<sup>a</sup> These are studies that include children or children and adolescents, but not studies that are limited to postpubertal adolescents.

## References

- Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. 2019. Available at: [https://aidsinfo.nih.gov/contentfiles/lvguidelines/oi\\_guidelines\\_Pediatrics.pdf](https://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_Pediatrics.pdf).
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2019. Available at: <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>.
- Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 2019. Available at: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.
- Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2018. Available at: [https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf).
- Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data: United States and 6 dependant areas, 2017. *HIV Surveillance Supplemental Report* 2019;24(3). Available at: <https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-report-vol-24-3.pdf>.
- Kapogiannis BG, Soe MM, Nesheim SR, et al. Mortality trends in the US perinatal AIDS collaborative transmission study (1986-2004). *Clin Infect Dis*. 2011;53(10):1024-1034. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22002982>.
- Mirani G, Williams PL, Chernoff M, et al. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis*. 2015;61(12):1850-1861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26270680>.
- Nesheim S, Taylor A, Lampe MA, et al. A framework for elimination of perinatal transmission of HIV in the United States. *Pediatrics*. 2012;130(4):738-744. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22945404>.
- Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection--United States, 2014. *MMWR Recomm Rep*. 2014;63(RR-03):1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24717910>.
- Flynn PM, Abrams EJ. Growing up with perinatal HIV. *AIDS*. 2019;33(4):597-603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30531318>.

11. Penazzato M, Gnanashanmugam D, Rojo P, et al. Optimizing research to speed up availability of pediatric antiretroviral drugs and formulations. *Clin Infect Dis*. 2017;64(11):1597-1603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29190337>.
12. Nesheim SR, Linley L, Gray KM, et al. Country of birth of children with diagnosed HIV infection in the United States, 2008-2014. *J Acquir Immune Defic Syndr*. 2018;77(1):23-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29040167>.
13. Wolf ER, Beste S, Barr E, et al. Health outcomes of international HIV-infected adoptees in the US. *Pediatr Infect Dis J*. 2016;35(4):422-427. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26629872>.
14. Committee On Pediatric AIDS. Transitioning HIV-infected youth into adult health care. *Pediatrics*. 2013;132(1):192-197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23796739>.
15. Cervia JS. Addressing the needs of youth with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis*. 2016;62(7):947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26743091>.
16. de Martino M, Galli L, Chiappini E. Perinatal human immunodeficiency virus type-1 in the 21st century: new challenges in treatment and health care organization. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S1-2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25894972>.
17. Judd A, Sohn AH, Collins IJ. Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care: moving on up. *Curr Opin HIV AIDS*. 2016;11(5):477-486. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27272537>.
18. Little KM, Taylor AW, Borkowf CB, et al. Perinatal antiretroviral exposure and prevented mother-to-child HIV infections in the era of antiretroviral prophylaxis in the United States, 1994-2010. *Pediatr Infect Dis J*. 2017;36(1):66-71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27749662>.
19. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/13679531>.
20. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics*. 2011;128(5):e1242-1249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22025597>.
21. Murphy D. Extrapolation of efficacy in the pediatric population. 2012. Available at: <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM340587.pdf>.
22. Food and Drug Administration. E11(R1) addendum: clinical investigation of medicinal products in the pediatric population guidance for industry. 2018. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM530012.pdf>.

# Maternal HIV Testing and Identification of Perinatal HIV Exposure

(Last updated December 24, 2019; last reviewed December 24, 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](#) from the Centers for Disease Control and Prevention [CDC]) **(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  $\geq 1$  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 from CDC](#)) **(AII)**.
- Expedited HIV testing should be performed during labor or delivery 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)**. The mother should not breastfeed unless supplemental HIV testing is negative **(AII)**. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) for guidance.
- Women who were not tested for HIV before or during labor should undergo expedited HIV antibody testing during the immediate postpartum period (or their newborns should undergo expedited HIV antibody testing) **(AII)**. 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)**. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) for guidance.
- Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
- HIV testing is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown **(AIII)**.

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

**Rating of Evidence:** I = One or more randomized trials in children<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> 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.<sup>1-5</sup> All HIV testing should be performed in a manner that is consistent with state and local laws. 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.<sup>2</sup> The “opt-out” approach during pregnancy is allowed in some jurisdictions.<sup>6</sup> The “opt-in” approach involves obtaining specific consent before testing, and this approach has been associated with lower testing rates.<sup>7,8</sup> The mandatory newborn HIV testing approach, which has been adopted by several states, involves testing newborns with or without maternal consent. In some areas, this applies to all newborns; in others, it applies only to the infants of mothers who have declined prenatal or intrapartum testing.

Partners of pregnant 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,<sup>9</sup> clinicians can also initiate a discussion about preventative interventions, including [pre-exposure prophylaxis](#), if the pregnant woman does not have HIV but is **at high risk for HIV acquisition**.

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

Providers should be aware that gaps in maternal HIV testing do occur and can contribute to missed opportunities for preventing perinatal HIV transmission.<sup>11-14</sup> Maternal HIV testing should be performed as early as possible during pregnancy, **wherever a woman seeks care (including emergency departments and prenatal clinics), to avoid missed opportunities to identify pregnant women with HIV**. Repeat HIV testing should be performed 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 who present to care in labor should be tested during delivery or as soon as possible after delivery.<sup>11-14</sup>

Determining antenatal maternal HIV status enables:

- Women 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;<sup>2,15,16</sup>
- **Referral of partners for testing, which allows them to initiate treatment if the results are positive or preventive interventions if the results are negative;**
- Provision of ART to the mother during pregnancy and labor, and provision of an appropriate antiretroviral (ARV) drug regimen to the newborn to reduce the risk of perinatal transmission;
- Counseling of women with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce the risk of perinatal transmission of HIV;<sup>17-19</sup>
- Counseling of women with HIV about the risks of HIV transmission through breast milk (breastfeeding is not recommended for women with HIV living in the United States);<sup>20</sup> and
- Early diagnostic evaluation of infants exposed to HIV (see [Diagnosis of HIV Infection in Infants and Children](#)), as well as testing of other children, to permit prompt initiation of ART and any indicated prophylaxis measures.<sup>1,21-23</sup>

**New technology has made it possible to detect HIV earlier and has reduced the performance time for laboratory-based assays, which can now be completed in <1 hour**. Accordingly, the Panels now base their

recommendations for HIV testing on [CDC's 2014 Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations](#).<sup>24</sup> The guidelines recommend that clinicians initiate HIV testing with an immunoassay that is capable of detecting HIV-1 antibodies, HIV-2 antibodies, and HIV-1 p24 antigen (referred to as an antigen/antibody combination immunoassay). Individuals with a reactive antigen/antibody combination immunoassay should be tested further with an HIV-1/HIV-2 antibody differentiation assay (referred to as supplemental testing). Individuals with a reactive antigen/antibody combination immunoassay and a nonreactive differentiation test should be tested with a Food and Drug Administration-approved plasma HIV RNA assay to establish a diagnosis of acute HIV infection (see CDC's [Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens](#)).

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

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

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

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

### ***Repeat HIV Testing in the Third Trimester***

Repeat HIV testing during the third trimester, before 36 weeks gestation, is recommended (see [Acute HIV Infection](#))<sup>25</sup> for pregnant women with negative results on their initial HIV antibody tests who:<sup>5</sup>

- Are 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 a **suspected or diagnosed** sexually transmitted infection during pregnancy); *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).<sup>2,26-28</sup>

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester. **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.**<sup>24,29</sup> **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 when indicated in areas where it is not routine. 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.<sup>14,30</sup> 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 cases, 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.<sup>30</sup> **Repeat HIV testing at other times during pregnancy should also be considered when clinically indicated. For example, repeat testing should be performed when a woman presents with symptoms that are suggestive of a sexually transmitted infection (STI), when a woman presents with a confirmed STI diagnosis, or when a woman presents with symptoms that are consistent with acute HIV infection.**

## 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 for fetal/infant prophylaxis (see [Intrapartum Antiretroviral Therapy/Prophylaxis](#)) and in developing an appropriate ARV regimen for infants who are at high risk of perinatal HIV transmission (see [Table 11](#)).<sup>1-3,21,27,31,32</sup>

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 for 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.<sup>24</sup> Immediate initiation of maternal intravenous intrapartum zidovudine is recommended to prevent perinatal transmission of HIV pending the supplemental result (see [Intrapartum Antiretroviral Therapy/Prophylaxis](#)).<sup>1-4,21,27</sup> 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 HIV Infection](#) or contact the [National Perinatal HIV Hotline](#)). No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay, unless acute HIV infection is suspected (see [Acute HIV Infection](#)).<sup>24</sup>

## 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. **Maternal testing should be done using the antigen/antibody combination immunoassay to screen for established and acute HIV; results should be obtained in <1 hour. If acute HIV infection is a possibility, then a plasma HIV RNA test should be sent as well.** When mothers are unavailable for testing, their newborns should undergo expedited HIV testing using the antigen/antibody combination immunoassay.<sup>1,21,27</sup> 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 HIV Infection](#)). 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 using the antigen/antibody combination immunoassay is indicated to identify HIV exposure and possible infection in these infants or children.<sup>1</sup> Mechanisms should be developed to facilitate prompt HIV screening for infants who have been abandoned and who 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.<sup>9</sup> 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](#)). Women who have acute HIV during pregnancy or lactation have an increased risk of perinatal transmission and secondary sexual transmission of HIV (see [Acute HIV Infection](#)).<sup>25,33-36</sup> **The antigen/antibody combination immunoassay will detect acute HIV infection earlier than other immunoassays, within approximately 15 days of acquisition. When acute HIV infection is suspected, a plasma HIV RNA test should be sent as well, because virologic tests can detect the presence of HIV approximately 5 days earlier than the antigen/antibody combination immunoassay.** Women with possible acute HIV infection who are breastfeeding should cease breastfeeding immediately until HIV infection is confirmed or excluded.<sup>20</sup> Breast milk can be expressed 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 [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.

## **References**

1. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics*. 2008;122(5):1127-1134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18977995>.
2. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; quiz CE11-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16988643>.

3. Chou R, Cantor AG, Zakher B, Bougatsos C. Screening for HIV in pregnant women: systematic review to update the 2005 U.S. Preventive services task force recommendation. *Ann Intern Med.* 2012;157(10):719-728. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23165663>.
4. U.S. Preventive Services Task Force. Screening for HIV: recommendation statement. 2013. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm>.
5. American College of Obstetrics and Gynecology: Committee on Obstetric Practice, HIV Expert Work Group. ACOG committee opinion No. 752: prenatal and perinatal human immunodeficiency virus testing. *Obstet Gynecol.* 2018;132(3):e138-e142. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30134428>.
6. Clinical Consultation Center. Compendium of state HIV testing laws. Perinatal quick reference guide: a guide to states' perinatal HIV testing laws for clinicians. 2011. Available at: [http://nccc.ucsf.edu/wp-content/uploads/2014/03/State\\_HIV\\_Testing\\_Laws\\_Perinatal\\_Quick\\_Reference.pdf](http://nccc.ucsf.edu/wp-content/uploads/2014/03/State_HIV_Testing_Laws_Perinatal_Quick_Reference.pdf).
7. Boer K, Smit C, van der Flier M, de Wolf F, Athena cohort study group. The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy. *Eur J Public Health.* 2011;21(5):632-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21051473>.
8. Yudin MH, Moravac C, Shah RR. Influence of an "opt-out" test strategy and patient factors on human immunodeficiency virus screening in pregnancy. *Obstet Gynecol.* 2007;110(1):81-86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17601900>.
9. Thomson KA, Hughes J, Baeten JM, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. *J Infect Dis.* 2018;218(1):16-25. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29514254>.
10. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. Available at: <https://stacks.cdc.gov/view/cdc/23447>.
11. Whitmore SK, Taylor AW, Espinoza L, Shouse RL, Lampe MA, Nesheim S. Correlates of mother-to-child transmission of HIV in the United States and Puerto Rico. *Pediatrics.* 2012;129(1):e74-81. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22144694>.
12. Ezeanolue EE, Pharr JR, Hunt A, Patel D, Jackson D. Why are children still being infected with HIV? Impact of an integrated public health and clinical practice intervention on mother-to-child HIV transmission in Las Vegas, Nevada, 2007-2012. *Ann Med Health Sci Res.* 2015;5(4):253-259. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26229713>.
13. Taylor AW, Nesheim SR, Zhang X, et al. Estimated perinatal HIV infection among infants born in the United States, 2002-2013. *JAMA Pediatr.* 2017;171(5):435-442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28319246>.
14. Liao C, Golden WC, Anderson JR, Coleman JS. Missed opportunities for repeat HIV testing in pregnancy: implications for elimination of mother-to-child transmission in the United States. *AIDS Patient Care STDS.* 2017;31(1):20-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27936863>.
15. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365(6):493-505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21767103>.
16. Baggaley RF, White RG, Hollingsworth TD, Boily MC. Heterosexual HIV-1 infectiousness and antiretroviral use: systematic review of prospective studies of discordant couples. *Epidemiology.* 2013;24(1):110-121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23222513>.
17. Jamieson DJ, Read JS, Kourtis AP, Durant TM, Lampe MA, Dominguez KL. Cesarean delivery for HIV-infected women: recommendations and controversies. *Am J Obstet Gynecol.* 2007;197(3 Suppl):S96-100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17825656>.
18. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/mL at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis.* 2010;50(4):585-596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20070234>.
19. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006. *AIDS.* 2008;22(8):973-981. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18453857>.

20. Committee On Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23359577>.
21. Havens PL, Mofenson LM, American Academy of Pediatrics Committee on Pediatric AIDS. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics*. 2009;123(1):175-187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19117880>.
22. Hegazi A, Forsyth S, Prime K, Bashh Adolescent Special Interest Group. Testing the children of HIV-infected parents: 6 years on from 'don't forget the children'. *Sex Transm Infect*. 2015;91(2):76-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25316913>.
23. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2018. Available at: [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf).
24. Branson BM, Owen SM, Wesolowski LG, et al. Laboratory testing for the diagnosis of HIV infection: updated recommendations. Centers for Disease Control and Prevention. 2014. Available at: <https://www.medbox.org/laboratory-testing-for-the-diagnosis-of-hiv-infection-updated-recommendations/download.pdf>.
25. Birkhead GS, Pulver WP, Warren BL, Hackel S, Rodriguez D, Smith L. Acquiring human immunodeficiency virus during pregnancy and mother-to-child transmission in New York: 2002–2006. *Obstet Gynecol*. 2010;115(6):1247-1255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20502297>.
26. Sansom SL, Jamieson DJ, Farnham PG, Bulterys M, Fowler MG. Human immunodeficiency virus retesting during pregnancy: costs and effectiveness in preventing perinatal transmission. *Obstet Gynecol*. 2003;102(4):782-790. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14551009>.
27. American College of Obstetrics: Gynecology Committee on Obstetric Practice. ACOG committee opinion no. 418: prenatal and perinatal human immunodeficiency virus testing: expanded recommendations. *Obstet Gynecol*. 2008;112(3):739-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18757690>.
28. Richey LE, Halperin J. Acute human immunodeficiency virus infection. *Am J Medical Sci*. 2013;345(2):136-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23095473>.
29. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2018. Available at: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>.
30. Trepka MJ, Mukherjee S, Beck-Sague C, et al. Missed opportunities for preventing perinatal transmission of human immunodeficiency virus, Florida, 2007-2014. *South Med J*. 2017;110(2):116-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28158882>.
31. Yee LM, Miller ES, Statton A, et al. Sustainability of statewide rapid HIV testing in labor and delivery. *AIDS Behav*. 2018;22(2):538-544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28986656>.
32. Scott RK, Crochet S, Huang CC. Universal rapid human immunodeficiency virus screening at delivery: a cost-effectiveness analysis. *Infect Dis Obstet Gynecol*. 2018;2018:6024698. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29731602>.
33. Lockman S, Creek T. Acute maternal HIV infection during pregnancy and breast-feeding: substantial risk to infants. *J Infect Dis*. 2009;200(5):667-669. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19627246>.
34. Taha TE, James MM, Hoover DR, et al. Association of recent HIV infection and *in-utero* HIV-1 transmission. *AIDS*. 2011;25(11):1357-1364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21572305>.
35. Humphrey JH, Marinda E, Mutasa K, et al. Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study. *BMJ*. 2010;341:c6580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21177735>.
36. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. *PLoS Med*. 2014;11(2):e1001608. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24586123>.

## Diagnosis of HIV Infection in Infants and Children (Last updated December 24, 2019; last reviewed December 24, 2019)

### Panel's Recommendations

- Virologic assays (i.e., HIV RNA or HIV DNA nucleic acid tests [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged <18 months with perinatal and postnatal HIV exposure; HIV antibody tests should not be used **(AII)**.
- HIV RNA or HIV DNA NATs are generally equally recommended **(AII)**.
- An assay that detects HIV non-B subtype viruses or Group O infections (e.g., an HIV RNA NAT or a dual-target total DNA/RNA test) is recommended for use in infants and children who were born to mothers with known or suspected non-B subtype virus or Group O infections **(AII)**. If a mother of an infant acquired HIV outside of the United States and has had repeated undetectable HIV RNA by standard testing, consultation with a clinical virologist on more sensitive HIV nucleic acid testing may be indicated.
- Virologic diagnostic testing (see Figure 1 and 2) is recommended for all infants with perinatal HIV exposure at the following ages:
  - 14 to 21 days **(AII)**
  - 1 to 2 months **(AII)**
  - 4 to 6 months **(AII)**
- For infants who are at higher risk of perinatal HIV transmission, additional virologic diagnostic testing is recommended at birth **(AII)** and at 2 to 6 weeks after cessation of antiretroviral prophylaxis **(BII)**.
- A positive virologic test should be confirmed as soon as possible by repeat virologic testing **(AII)**.
- Definitive exclusion of HIV infection in nonbreastfed infants is based on two or more negative virologic tests, with one obtained at age  $\geq 1$  month and one at age  $\geq 4$  months, or two negative HIV antibody tests from separate specimens that were obtained at age  $\geq 6$  months **(AII)**.
- Some experts confirm the absence of HIV at age 12 to 18 months 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 remain HIV antibody-positive should be based on an HIV NAT and antibody retesting at 24 months **(AII)**.
- Diagnostic testing in children with nonperinatal exposure only or in 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 infection **(AII)**.

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

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

**Rating of Evidence:** I = One or more randomized trials in children<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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

## Diagnosis of HIV in Infants and Children

HIV can be definitively diagnosed by virologic testing in most nonbreastfed infants with perinatal HIV exposure by age 1 to 2 months, and in virtually all infants with HIV by age 4 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.<sup>1,2</sup> 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 repeat virologic testing, because false-positive results can occur with both RNA and DNA assays.<sup>3</sup> For additional information on the diagnosis of Group M non-subtype B, Group O HIV-1 infections, and HIV-2 infections, see the relevant sections below.

Antigen/antibody combination immunoassays that detect HIV-1/2 antibodies as well as HIV-1 p24 antigen **are not recommended** for diagnosis of HIV infection in infants. In the first months of life, the antigen component of antigen/antibody tests is less sensitive than an HIV NAT, and antibody tests should not be used for HIV diagnosis in infants and children <18 months of age.<sup>4,6</sup> Children with perinatal HIV exposure who are aged 18 to 24 months occasionally have residual maternal HIV antibodies; definitive confirmation of HIV infection in children in this age group who remain HIV antibody-positive should be based on a NAT **and antibody retesting at 24 months** (see the section below titled 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 the section below titled Diagnostic Testing in Children with Nonperinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months).<sup>1</sup>

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<sup>7</sup> and receive antiretroviral (ARV) prophylaxis or **presumptive** HIV therapy as soon as possible. For ARV management of newborns who have been exposed to HIV and newborns with HIV infection (including those who do not yet have confirmed infection), see [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#).<sup>8,9</sup>

## 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 and 2 summarize the timing of recommended virologic diagnostic testing for infants based on HIV transmission risk. Infants at higher risk on combination ARV prophylaxis regimens may require testing at additional time points (see Figure 1) compared to infants at low risk of transmission (see Figure 2). The risk of transmission is determined based on whether a mother is receiving antiretroviral therapy (ART) and virally suppressed.

HIV infection can be **presumptively** excluded in nonbreastfed infants with two or more negative virologic tests (one at age  $\geq 2$  weeks and one at age  $\geq 4$  weeks) or one negative virologic test (i.e., negative NAT [RNA or DNA]) at age  $\geq 8$  weeks, or one negative HIV antibody test at age  $\geq 6$  months.<sup>1,7</sup>

**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  $\geq 1$  month and one at age  $\geq 4$  months, or two negative HIV antibody tests from separate specimens obtained at age  $\geq 6$  months.

For both presumptive and definitive exclusion of HIV infection, a child must have no other laboratory evidence (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and must not be breastfeeding. 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.<sup>10</sup> Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see [Initial Postnatal Management of the Neonate Exposed to HIV](#) and the [Pediatric Opportunistic Infection Guidelines](#)).

The case definition for indeterminate HIV infection status is a child who has been exposed to HIV, who is 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 not having acquired HIV. This includes infants who do not meet the minimum requirement for presumptively uninfected.

### ***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,<sup>11-16</sup> 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 but did not have sustained viral suppression

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

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 Antiretroviral Guidelines](#)). Infants who have a positive virologic test result at or before age 48 hours are considered to have early (intrauterine) infection, whereas infants who have a negative virologic test result during the first week of life and subsequently have positive test results are considered to have late (intrapartum) infection.<sup>11,12,17</sup>

### ***Virologic Testing at Age 14 to 21 Days***

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,<sup>7</sup> 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 A in [When to Initiate Therapy in Antiretroviral-Naive Children](#) in the [Pediatric Antiretroviral Guidelines](#)).

### ***Virologic Testing at Age 1 to 3 Months***

Testing performed at age 1 to 2 months is intended to maximize the likelihood of detecting HIV infection in infants. **In the HPTN 040 study, 93 of 140 infants with HIV (66.4%) were identified at birth. Infants who received negative test results in the first 7 days of life received an HIV diagnosis when the next diagnostic test was performed at 3 months of age.**<sup>18</sup> 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 performing an additional virologic test 2 to 6 weeks after cessation of ARV prophylaxis **or presumptive HIV therapy** (i.e., at age 8–12 weeks), given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis **or presumptive HIV therapy**, may reduce the sensitivity of testing.<sup>7,18,19</sup> In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt recognition of infants with HIV, with an additional test at 8 to 12 weeks of life (i.e., 2 to 6 weeks after cessation of prophylaxis **or presumptive HIV therapy**) to capture additional cases (see Figure 1). 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 (see Figure 2).

An infant with two negative virologic test results (one at age  $\geq 14$  days and the other at age  $\geq 4$  weeks) or one negative test result at age  $\geq 8$  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, and is not breastfed.

## ***Virologic Testing at Age 4 to 6 Months***

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

### **Figure 1. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV and Who Are at Higher Risk of Perinatal HIV Transmission**

**Higher Risk:** Infants born to mothers with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARV drugs, received intrapartum ARV drugs only, 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.

Age at NAT testing	Birth	14–21 days	1–2 months	2–3 months <sup>a</sup>	4–6 months
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<sup>a</sup> For higher-risk infants, additional virologic diagnostic testing is recommended at birth and 2 to 6 weeks after cessation of ARV prophylaxis (i.e., at 8–12 weeks of life).

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

### **Figure 2. Recommended Virologic Testing Schedules for Infants Who Were Exposed to HIV and Who Are at Low Risk of Perinatal HIV Transmission**

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

Age at NAT testing	14–21 days	1–2 months <sup>a</sup>	4–6 months
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<sup>a</sup> Test may be timed to occur at least 2 weeks after cessation of ARV prophylaxis.

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

## ***Antibody Testing at Age 6 Months and Older***

Two or more negative results of HIV antibody tests that were performed in nonbreastfed infants at age  $\geq 6$  months can also be used to definitively exclude HIV infection in children with no clinical or virologic laboratory-documented evidence of HIV infection.<sup>20,21</sup>

## ***Antibody Testing at Age 12 to 18 Months to Document Seroreversion***

In cases where an infant or child has not previously received two negative antibody test results, some experts confirm the absence of HIV infection with negative virologic test results by repeating serologic testing between 12 months and 18 months of age to confirm that the maternal HIV antibodies that transferred *in utero* have cleared.<sup>1</sup> In a study from 2012, the median age at seroreversion was 13.9 months.<sup>22</sup> Although the majority of infants who do not have 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.<sup>22–25</sup>

## **Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations**

### ***Late Seroreversion (Aged $\leq 24$ Months)***

Nonbreastfed children with perinatal HIV exposure, no other HIV transmission risk factor, and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies up to age 24 months.

These children are called late seroreverters.<sup>22-25</sup> In one study, 14% of children with HIV exposure who did not have HIV seroreverted after age 18 months.<sup>22</sup> **More recent data from Thailand associated late seroreversion with the antenatal use of protease inhibitors in pregnant women with HIV. In this study, late seroreversion was also associated with the use of fourth-generation combination antigen/antibody immunoassays.**<sup>26</sup> These children may have had positive immunoassay results, but supplemental antibody test results 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 have a positive HIV antibody (or antigen/antibody) test at age 18 months to 24 months. **Virologic testing will distinguish late-seroreverting children who do not have HIV but who have residual antibodies from children who have antibodies due to underlying HIV infection. Antibody retesting at 24 months should also occur after a negative virologic test result.**

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

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

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

Children with non-subtype B HIV-1 and children with HIV-2 may have false-negative virologic tests but persistent positive immunoassay results and indeterminate HIV-1 Western blot results.<sup>27-29</sup> 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. Monitoring of infants born to women with HIV who opt to breastfeed after comprehensive counseling should include immediate HIV diagnostic virologic testing with a NAT at standard time points (see Figure 1). 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 (1-888-448-8765). See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and [Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed](#).<sup>30-32</sup>

### ***Premastication***

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

### ***Additional Routes of HIV Transmission***

Additional routes of HIV transmission in children include sexual abuse, receipt of contaminated blood products, and needlestick with contaminated needles. In such cases, maternal HIV status may be negative. If

the mother's 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 reported cases of HIV transmission from these activities have been documented.<sup>39</sup>

## ***Diagnostic Testing***

Diagnosis of HIV-1 infection in infants and children with nonperinatal HIV exposure only or children with perinatal HIV exposure who are aged >24 months relies primarily on HIV antibody and antigen/antibody tests.<sup>1,40</sup> 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. These tests are recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection. However, p24 antigen from HIV-1 non-B strains, HIV-1 non-M strains, and HIV-2 strains may not be detected.<sup>41</sup>
- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies. This immunoassay is recommended for supplemental testing.
- HIV-1 NAT. A NAT is always indicated as an additional test to diagnose acute HIV infection.
- HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests). These tests are alternatives for supplemental testing, but they will not detect HIV during acute infection. **These tests are rarely performed and not recommended by the Centers for Disease Control and Prevention (CDC) for HIV screening in the United States.**

Diagnosis of HIV-2 in children with nonperinatal exposure only or children with perinatal exposure aged >24 months relies on the 2014 CDC/Association of Public Health Laboratories laboratory testing guidelines. These guidelines recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that distinguishes between HIV-1 and HIV-2 antibodies for supplemental testing. When used as a supplemental test, the results of the HIV-1 Western blot are more ambiguous than those of the HIV-1/HIV-2 antibody differentiation immunoassay; >60% of individuals with HIV-2 are misclassified as having HIV-1 by the HIV-1 Western blot.<sup>1,42</sup> All HIV-2 cases should be reported to the HIV surveillance program of the state or local health department; additional HIV-2 DNA PCR testing can be arranged by a local public health laboratory or by CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is inconclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis, although this assay is not commercially available.<sup>43,44</sup>

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

### ***HIV RNA Assays***

HIV quantitative RNA assays detect extracellular viral RNA in plasma. Their specificity has been shown to be 100% at birth and at ages 1 month, 3 months, and 6 months and is comparable to the specificity of HIV DNA PCR.<sup>19</sup> 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.<sup>45,46</sup> Testing at birth will detect HIV RNA in infants who acquire HIV *in utero* and not in those who acquire HIV from exposure during delivery or immediately prior to delivery (i.e., during the intrapartum period). Studies have shown that HIV RNA assays identify 25% to 58% of infants with HIV infection from birth through the first week of life, 89% at age 1 month, and 90% to 100% by age 2 months to 3 months. These results are similar to the results of HIV DNA PCR for early diagnosis of HIV.<sup>3,7,19,47</sup>

HIV RNA undergoes reverse transcription in the cytoplasm to double-stranded DNA, which persists in the nucleus of an infected cell. The sensitivity of HIV RNA assays are affected by maternal antenatal ART or

infant combination ARV prophylaxis.<sup>48</sup> 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 who were receiving multidrug prophylaxis (n = 9; median HIV RNA 2.5 log<sub>10</sub> copies/mL) than those in infants who were receiving single-drug zidovudine (ZDV) prophylaxis (n = 47; median HIV RNA 5.4 log<sub>10</sub> copies/mL). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log<sub>10</sub> copies/mL) by age 3 months in both groups after stopping prophylaxis.<sup>19</sup> 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 (WHO).<sup>49</sup> Further studies are necessary to evaluate the sensitivity of HIV RNA assays in infants during receipt of multidrug ARV prophylaxis, whose mothers also receive antenatal ART.

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

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing. It is the only qualitative RNA test that is approved by the FDA.<sup>17,50-53</sup>

### ***HIV DNA PCR and Related Assays***

HIV DNA PCR is a sensitive technique that is used to detect intracellular HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at ages 1 month, 3 months, and 6 months. Studies have shown that HIV DNA PCR assays identify 20% to 55% of infants with HIV infection from birth through the first week of life, with the same caveat as for RNA testing—testing at birth 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 age 2 weeks to 4 weeks and to 100% at ages 3 months and 6 months.<sup>7,17,19,47</sup>

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 who were 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 that consisted of 6 weeks of ZDV 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 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.<sup>18</sup> Data from Thailand in nonbreastfed infants showed that a prophylactic regimen of ZDV plus lamivudine plus nevirapine for 6 weeks was associated with delayed HIV DNA detection. In this cohort, up to 20% of infants who were exposed to HIV had their first positive DNA PCR test result 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.<sup>54</sup>

A study from Cape Town evaluated the sensitivity of HIV DNA assays within 8 days of life, during and after initiating ART in infants with HIV. The infants had been exposed to a combination of maternal ART *in utero* and ARV drugs for prophylaxis and treatment. The authors noted that one infant had undetectable HIV DNA after 6 days on treatment, another had undetectable HIV DNA after 3 months, and a third had undetectable

HIV DNA after 4 months. In seven infants who achieved virologic suppression (defined as a continuous downward trend in plasma HIV RNA, with <100 copies/mL after 6 months), total HIV DNA continued to decay over 12 months. The authors suggested that rapid decline of HIV-1 RNA and DNA may complicate definitive diagnosis.<sup>55</sup> 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 showed that infants who received the WHO Option B+ regimen had fewer indeterminate DNA PCR results than infants who were receiving older regimens. These findings should be regarded with a high index of suspicion, since many patients had positive results that were representative of true HIV infections on subsequent samples. These findings point to the need for additional virologic testing to establish definitive diagnosis.<sup>56</sup> Another group of South African investigators reported similar conclusions in a study of a cohort of 5,743 neonates from Johannesburg who were exposed to HIV.<sup>57</sup>

The AMPLICOR<sup>®</sup> HIV-1 DNA test has been widely used for diagnosis of HIV in infants born to mothers with HIV-1 infection since it was introduced in 1992. However, it is no longer commercially available in the United States. The sensitivity and specificity of noncommercial HIV-1 DNA tests that use individual laboratory reagents may differ from the sensitivity and specificity of an FDA-approved commercial test. The COBAS<sup>®</sup> AmpliPrep/COBAS<sup>®</sup> TaqMan<sup>®</sup> HIV-1 **version 2.0** qualitative test (which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots) may be used for HIV diagnosis in infants, but is not approved by the FDA.<sup>57-59</sup> **The sensitivity of these DNA assays may be lower than the sensitivity of RNA assays in children who are not currently being treated with ARV drugs.**

**These considerations underscore the importance of testing with HIV NATs at 4 months, well after neonatal prophylaxis has stopped, and highlights the utility of antibody retesting at 24 months of life.**

## 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.<sup>60</sup> 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.<sup>61</sup> In an evaluation of infants who received a perinatal HIV infection diagnosis in New York State in 2001 and 2002, 16.7% of infants had acquired a non-subtype B strain of HIV, compared with 4.4% of infants born in 1998 and 1999.<sup>62</sup> Among a group of 40 children who visited a pediatric HIV clinic in Rhode Island between 1991 and 2012, 14 (35%) acquired HIV with non-B HIV-1 subtypes. All 14 children were either born outside the United States or their parents were of foreign origin.<sup>63</sup> In an analysis of 1,277 unique sequences collected in Rhode Island from 2004 to 2011, 8.3% were non-B subtypes (including recombinant forms). Twenty-two percent of participants with non-B subtypes formed transmission clusters, including individuals with perinatally acquired infection.<sup>64</sup> In an analysis of 3,895 HIV-1 sequences that were collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms).

Evolving immigration patterns may be contributing to local and regional increases in HIV-1 subtype diversity. Non-subtype B viruses predominate in other parts of the world, such as subtype C in regions of Africa and India and subtype CRF01 in much of Southeast Asia. Group O HIV strains are seen in West-Central Africa.<sup>65</sup> Non-subtype B and Group O strains may be seen in countries with links to these geographical regions.<sup>66-70</sup> The geographical distribution of HIV groups is available at the [HIV Sequence Database](#).

Real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay are better at detecting non-subtype B HIV infection and the less-common Group O strains than older RNA assays.<sup>71-76</sup> (see [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#)). The COBAS<sup>®</sup> AmpliPrep/COBAS<sup>®</sup> TaqMan<sup>®</sup> HIV-1 qualitative test (a dual-target DNA/RNA test) can identify non-subtype B and Group O infections.<sup>58,59</sup>

Thus, a real-time PCR assay, qualitative RNA assay, or a dual-target total DNA/RNA test should be used for infant testing instead of a DNA PCR assay when evaluating an infant born to a mother whose HIV infection is linked to an area that is endemic for non-subtype B HIV or Group O strains, such as Africa or Southeast Asia. Another indication is when initial testing is negative using a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody test results obtained at age  $\geq 6$  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 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.<sup>77-79</sup> Infection is well documented in France and Portugal, which have large numbers of immigrants from these regions.<sup>80,81</sup> HIV-1 and HIV-2 coinfection may occur, but is rarely described outside areas where HIV-2 is endemic. HIV-2 is rare in the United States. Although accurately diagnosing HIV-2 can be difficult, it is clinically important because HIV-2 strains are resistant to several ARV drugs that were developed to suppress HIV-1.<sup>82-84</sup> (See [HIV-2 Infection and Pregnancy](#).)

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 that is endemic for HIV-2 infection or if her HIV test results are suggestive of HIV-2 infection (i.e., the mother has a positive initial HIV 1/2 immunoassay test result, 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 is to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing, as the results of this test are less ambiguous than the results of the HIV-1 Western blot when it is used as a supplemental test.<sup>1,85</sup> 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.<sup>43,44</sup> Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.<sup>77,86</sup>

## **References**

1. Centers for Disease Control and Prevention and the Association of Public Health Laboratories. Laboratory testing for the diagnosis of HIV infection: updated recommendations. 2014. Available at: <http://dx.doi.org/10.15620/cdc.23447>.
2. Donovan M, Palumbo P. Diagnosis of HIV: challenges and strategies for HIV prevention and detection among pregnant women and their infants. *Clin Perinatol*. 2010;37(4):751-763, viii. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21078448>.
3. Read JS, Committee on Pediatric AIDS, American Academy of Pediatrics. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. *Pediatrics*. 2007;120(6):e1547-1562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18055670>.
4. Tamhane M, Gautney B, Shiu C, et al. Analysis of the optimal cut-point for HIV-p24 antigen testing to diagnose HIV infection in HIV-exposed children from resource-constrained settings. *J Clin Virol*. 2011;50(4):338-341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21330193>.
5. Wessman MJ, Theilgaard Z, Katzenstein TL. Determination of HIV status of infants born to HIV-infected mothers: a review of the diagnostic methods with special focus on the applicability of p24 antigen testing in developing countries. *Scandinavian J Infect Dis*. 2012;44(3):209-215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22074445>.
6. Bhowan K, Sherman GG. Performance of the first fourth-generation rapid human immunodeficiency virus test in children. *Pediatr Infect Dis J*. 2013;32(5):486-488. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23190776>.

7. Havens PL, Mofenson LM, American Academy of Pediatrics Committee on Pediatric AIDS. Evaluation and management of the infant exposed to HIV-1 in the United States. *Pediatrics*. 2009;123(1):175-187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19117880>.
8. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J*. 2011;30(5):408-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21266939>.
9. Sollai S, Noguera-Julian A, Galli L, et al. Strategies for the prevention of mother to child transmission in Western countries: an update. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S14-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25894973>.
10. Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. 2019. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi\\_guidelines\\_pediatrics.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf).
11. Lilian RR, Kalk E, Technau KG, Sherman GG. Birth diagnosis of HIV infection on infants to reduce infant mortality and monitor for elimination of mother-to-child transmission. *Pediatr Infect Dis J*. 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23574775>.
12. Jourdain G, Mary JY, Coeur SL, et al. Risk factors for *in utero* or intrapartum mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. *J Infect Dis*. 2007;196(11):1629-1636. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18008246>.
13. Tubiana R, Le Chenadec J, Rouzioux C, et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS CO1). *Clin Infect Dis*. 2010;50(4):585-596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20070234>.
14. Katz IT, Shapiro DE, Tuomala R. Factors associated with lack of viral suppression at delivery. *Ann Intern Med*. 2015;162(12):874-875. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26075762>.
15. Momplaisir FM, Brady KA, Fekete T, Thompson DR, Diez Roux A, Yehia BR. Time of HIV diagnosis and engagement in prenatal care impact virologic outcomes of pregnant women with HIV. *PLoS One*. 2015;10(7):e0132262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26132142>.
16. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis*. 2015;61(11):1715-1725. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26197844>.
17. Lilian RR, Kalk E, Bhowan K, et al. Early diagnosis of *in utero* and intrapartum HIV infection in infants prior to 6 weeks of age. *J Clin Microbiol*. 2012;50(7):2373-2377. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22518871>.
18. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716975>.
19. Burgard M, Blanche S, Jasseron C, et al. Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. *J Pediatr*. 2012;160(1):60-66 e61. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21868029>.
20. Kuhn L, Schramm DB, Shiau S, et al. Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed. *AIDS*. 2015;29(9):1053-1060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25870988>.
21. Payne H, Mkhize N, Otjombe K, et al. Reactivity of routine HIV antibody tests in children who initiated antiretroviral therapy in early infancy as part of the children with HIV early antiretroviral therapy (CHER) trial: a retrospective analysis. *Lancet Infect Dis*. 2015;15(7):803-809. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26043884>.
22. Gutierrez M, Ludwig DA, Khan SS, et al. Has highly active antiretroviral therapy increased the time to seroreversion in HIV exposed but uninfected children? *Clin Infect Dis*. 2012;55(9):1255-1261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22851494>.

23. Gulia J, Kumwenda N, Li Q, Taha TE. HIV seroreversion time in HIV-1-uninfected children born to HIV-1-infected mothers in Malawi. *J Acquir Immune Defic Syndr*. 2007;46(3):332-337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17786126>.
24. Alcantara KC, Pereira GA, Albuquerque M, Stefani MM. Seroreversion in children born to HIV-positive and AIDS mothers from Central West Brazil. *Trans R Soc Trop Med Hyg*. 2009;103(6):620-626. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19339030>.
25. Sohn AH, Thanh TC, Thinh le Q, et al. Failure of human immunodeficiency virus enzyme immunoassay to rule out infection among polymerase chain reaction-negative Vietnamese infants at 12 months of age. *Pediatr Infect Dis J*. 2009;28(4):273-276. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19289981>.
26. Chatpornvorarux S, Maleesatharn A, Rungmaitree S, et al. Delayed seroreversion in HIV-exposed uninfected infants. *Pediatr Infect Dis J*. 2019;38(1):65-69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30239474>.
27. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J*. 2002;21(9):885-886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12380591>.
28. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis*. 2002;34(3):417-418. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11774090>.
29. Obaro SK, Losikoff P, Harwell J, Pugatch D. Failure of serial human immunodeficiency virus type 1 DNA polymerase chain reactions to identify human immunodeficiency virus type 1 clade A/G. *Pediatr Infect Dis J*. 2005;24(2):183-184. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15702052>.
30. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 2019. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.
31. Committee On Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics*. 2013;131(2):391-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23359577>.
32. King CC, Kourtis AP, Persaud D, et al. Delayed HIV detection among infants exposed to postnatal antiretroviral prophylaxis during breastfeeding. *AIDS*. 2015;29(15):1953-1961. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26153671>.
33. Centers for Disease Control and Prevention. Premastication of food by caregivers of HIV-exposed children--nine U.S. sites, 2009-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(9):273-275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21389930>.
34. Gaur AH, Freimanis-Hance L, Dominguez K, et al. Knowledge and practice of prechewing/prewarming food by HIV-infected women. *Pediatrics*. 2011;127(5):e1206-1211. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21482608>.
35. Hafeez S, Salami O, Alvarado M, Maldonado M, Purswani M, Haggmann S. Infant feeding practice of premastication: an anonymous survey among human immunodeficiency virus-infected mothers. *Arch Pediatr Adolesc Med*. 2011;165(1):92-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21199989>.
36. Maritz ER, Kidd M, Cotton MF. Premasticating food for weaning African infants: a possible vehicle for transmission of HIV. *Pediatrics*. 2011;128(3):e579-590. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21873699>.
37. Ivy W, 3rd, Dominguez KL, Rakhmanina NY, et al. Premastication as a route of pediatric HIV transmission: case-control and cross-sectional investigations. *J Acquir Immune Defic Syndr*. 2012;59(2):207-212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22027873>.
38. Gaur AH, Cohen RA, Read JS, et al. Prechewing and prewarming food for HIV-exposed children: a prospective cohort experience from Latin America. *AIDS Patient Care STDS*. 2013;27(3):142-145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23477456>.

39. Centers for Disease Control and Prevention. HIV transmission 2018. Available at: <https://www.cdc.gov/hiv/basics/transmission.html>. 2018.
40. Alexander TS. Human immunodeficiency virus diagnostic testing: 30 years of evolution. *Clin Vaccine Immunol*. 2016;23(4):249-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26936099>.
41. Ly TD, Plantier JC, Leballais L, Gonzalo S, Lemee V, Laperche S. The variable sensitivity of HIV Ag/Ab combination assays in the detection of p24Ag according to genotype could compromise the diagnosis of early HIV infection. *J Clin Virol*. 2012;55(2):121-127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22795598>.
42. Centers for Disease Control and Prevention. HIV-2 Infection Surveillance—United States, 1987-2009. *MMWR Morb Mortal Wkly Rep*. 2011;60(29):985-988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21796096>.
43. Shanmugam V, Switzer WM, Nkengasong JN, et al. Lower HIV-2 plasma viral loads may explain differences between the natural histories of HIV-1 and HIV-2 infections. *J Acquir Immune Defic Syndr*. 2000;24(3):257-263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10969350>.
44. Damond F, Benard A, Balotta C, et al. An international collaboration to standardize HIV-2 viral load assays: results from the 2009 ACHI(E)V(2E) quality control study. *J Clin Microbiol*. 2011;49(10):3491-3497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21813718>.
45. Lilian RR, Bhowan K, Sherman GG. Early diagnosis of human immunodeficiency virus-1 infection in infants with the NucliSens EasyQ assay on dried blood spots. *J Clin Virol*. 2010;48(1):40-43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20211580>.
46. Patel JA, Anderson EJ, Dong J. False positive ultrasensitive HIV bDNA viral load results in diagnosis of perinatal HIV-infection in the era of low transmission. *Laboratory Medicine*. 2009;40(10):611-614. Available at: <http://labmed.oxfordjournals.org/content/40/10/611>.
47. American Academy of Pediatrics Committee on Pediatric AIDS. HIV testing and prophylaxis to prevent mother-to-child transmission in the United States. *Pediatrics*. 2008;122(5):1127-1134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18977995>.
48. Saitoh A, Hsia K, Fenton T, et al. Persistence of human immunodeficiency virus (HIV) type 1 DNA in peripheral blood despite prolonged suppression of plasma HIV-1 RNA in children. *J Infect Dis*. 2002;185(10):1409-1416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11992275>.
49. Mazanderani AH, Moyo F, Kufa T, Sherman GG. Brief Report: Declining baseline viremia and escalating discordant HIV-1 confirmatory results within South Africa's early infant diagnosis program, 2010-2016. *J Acquir Immune Defic Syndr*. 2018;77(2):212-216. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29084045>.
50. Food and Drug Administration. APTIMA HIV-1 RNA qualitative assay. 2006. Available at: <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm149922.htm>.
51. Pierce VM, Neide B, Hodinka RL. Evaluation of the gen-probe aptima HIV-1 RNA qualitative assay as an alternative to Western blot analysis for confirmation of HIV infection. *J Clin Microbiol*. 2011;49(4):1642-1645. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21346052>.
52. Fiscus SA, McMillion T, Nelson JA, Miller WC. Validation of the gen-probe aptima qualitative HIV-1 RNA assay for diagnosis of human immunodeficiency virus infection in infants. *J Clin Microbiol*. 2013;51(12):4137-4140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24088864>.
53. Nelson JA, Hawkins JT, Schanz M, et al. Comparison of the gen-probe aptima HIV-1 and abbot HIV-1 qualitative assays with the roche amplicor HIV-1 DNA assay for early infant diagnosis using dried blood spots. *J Clin Virol*. 2014;60(4):418-421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24929752>.
54. Puthankit T, Rojanwivat T. Delayed HIV DNA PCR detection among infants received combination ART prophylaxis. Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA
55. Veldsman KA, Maritz J, Isaacs S, et al. Rapid decline of HIV-1 DNA and RNA in infants starting very early

- antiretroviral therapy may pose a diagnostic challenge. *AIDS*. 2018;32(5):629-634. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29334551>.
56. Maritz J, Maharaj JN, Cotton MF, Preiser W. Interpretation of indeterminate HIV-1 PCR results are influenced by changing vertical transmission prevention regimens. *J Clin Virol*. 2017;95:86-89. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28898704>.
  57. Technau KG, Mazanderani AH, Kuhn L, et al. Prevalence and outcomes of HIV-1 diagnostic challenges during universal birth testing - an urban South African observational cohort. *J Int AIDS Soc*. 2017;20(Suppl 6):21761. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28872276>.
  58. Templer SP, Seiverth B, Baum P, Stevens W, Seguin-Devaux C, Carmona S. Improved sensitivity of a dual-target HIV-1 qualitative test for plasma and dried blood spots. *J Clin Microbiol*. 2016;54(7):1877-1882. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27194686>.
  59. Mossoro-Kpinde CD, Jenabian MA, Gody JC, et al. Evaluation of the upgraded version 2.0 of the Roche COBAS((R)) AmpliPrep/COBAS((R)) TaqMan HIV-1 qualitative assay in Central African children. *Open AIDS J*. 2016;10:158-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27857825>.
  60. Pyne MT, Hackett J Jr, Holzmayer V, Hillyard DR. Large-scale analysis of the prevalence and geographic distribution of HIV-1 non-B variants in the United States. *J Clin Microbiol*. 2013;51(8):2662-2669. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23761148>.
  61. Nesheim SR, Linley L, Gray KM, et al. Country of birth of children with diagnosed HIV infection in the United States, 2008-2014. *J Acquir Immune Defic Syndr*. 2018;77(1):23-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29040167>.
  62. Karchava M, Pulver W, Smith L, et al. Prevalence of drug-resistance mutations and non-subtype B strains among HIV-1 infected infants from New York State. *J Acquir Immune Defic Syndr*. 2006;42(5):614-619. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16868498>.
  63. Rogo T, DeLong AK, Chan P, Kantor R. Antiretroviral treatment failure, drug resistance, and subtype diversity in the only pediatric HIV clinic in Rhode Island. *Clin Infect Dis*. 2015;60(9):1426-1435. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25637585>.
  64. Chan PA, Reitsma MB, DeLong A, et al. Phylogenetic and geospatial evaluation of HIV-1 subtype diversity at the largest HIV center in Rhode Island. *Infect Genet Evol*. 2014;28:358-366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24721515>.
  65. Bush S, Tebit DM. HIV-1 group O origin, evolution, pathogenesis, and treatment: unraveling the complexity of an outlier 25 years later. *AIDS reviews*. 2015;17(3):147-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26450803>.
  66. Auwanit W, Isarangkura-Na-Ayuthaya P, Kasornpikul D, Ikuta K, Sawanpanyalert P, Kameoka M. Detection of drug resistance-associated and background mutations in human immunodeficiency virus type 1 CRF01\_AE protease and reverse transcriptase derived from drug treatment-naive patients residing in central Thailand. *AIDS Res Hum Retroviruses* 2009;25(6):625-631. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19500016>.
  67. Deshpande A, Jauvin V, Pinson P, Jeannot AC, Fleury HJ. Phylogenetic analysis of HIV-1 reverse transcriptase sequences from 382 patients recruited in JJ Hospital of Mumbai, India, between 2002 and 2008. *AIDS Res Hum Retroviruses*. 2009;25(6):633-635. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19534630>.
  68. Chaix ML, Seng R, Frange P, et al. Increasing HIV-1 non-B subtype primary infections in patients in France and effect of HIV subtypes on virological and immunological responses to combined antiretroviral therapy. *Clin Infect Dis*. 2013;56(6):880-887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23223603>.
  69. Hemelaar J, Gouws E, Ghys PD, Osmanov S, Who-Unaided Network for HIV Isolation Characterisation. Global trends in molecular epidemiology of HIV-1 during 2000-2007. *AIDS*. 2011;25(5):679-689. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21297424>.
  70. Dauwe K, Mortier V, Schauvliege M, et al. Characteristics and spread to the native population of HIV-1 non-B subtypes in two European countries with high migration rate. *BMC Infect Dis*. 2015;15:524. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25637585>.

[nih.gov/pubmed/26572861](http://www.ncbi.nlm.nih.gov/pubmed/26572861).

71. Church D, Gregson D, Lloyd T, et al. Comparison of the RealTime HIV-1, COBAS TaqMan 48 v1.0, Easy Q v1.2, and Versant v3.0 assays for determination of HIV-1 viral loads in a cohort of Canadian patients with diverse HIV subtype infections. *J Clin Microbiol*. 2011;49(1):118-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21084515>.
72. Cobb BR, Vaks JE, Do T, Vilchez RA. Evolution in the sensitivity of quantitative HIV-1 viral load tests. *J Clin Virol*. 2011;52 Suppl 1:S77-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22036041>.
73. Katsoulidou A, Rokka C, Issaris C, et al. Comparative evaluation of the performance of the abbot realtime HIV-1 assay for measurement of HIV-1 plasma viral load on genetically diverse samples from Greece. *Virology*. 2011;8:10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21219667>.
74. Gueudin M, Leoz M, Lemee V, et al. A new real-time quantitative PCR for diagnosis and monitoring of HIV-1 group O infection. *J Clin Microbiol*. 2012;50(3):831-836. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22170927>.
75. Xu S, Song A, Nie J, et al. Comparison between the automated Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 test version 2.0 assay and its version 1 and Nuclisens HIV-1 EasyQ version 2.0 assays when measuring diverse HIV-1 genotypes in China. *J Clin Virol*. 2012;53(1):33-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22051503>.
76. Muenchhoff M, Madurai S, Hempenstall AJ, et al. Evaluation of the NucliSens EasyQ v2.0 assay in comparison with the Roche Amplicor v1.5 and the Roche CAP/CTM HIV-1 Test v2.0 in quantification of C-clade HIV-1 in plasma. *PLoS One*. 2014;9(8):e103983. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25157919>.
77. Torian LV, Eavey JJ, Punsalang AP, et al. HIV type 2 in New York City, 2000–2008. *Clin Infect Dis*. 2010;51(11):1334-1342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21039219>.
78. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. *Clin Infect Dis*. 2011;52(6):780-787. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21367732>.
79. Prince PD, Matser A, van Tienen C, Whittle HC, Schim van der Loeff MF. Mortality rates in people dually infected with HIV-1/2 and those infected with either HIV-1 or HIV-2: a systematic review and meta-analysis. *AIDS*. 2014;28(4):549-558. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23921613>.
80. Barin F, Cazein F, Lot F, et al. Prevalence of HIV-2 and HIV-1 group O infections among new HIV diagnoses in France: 2003-2006. *AIDS*. 2007;21(17):2351-2353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18090288>.
81. Thiebaut R, Matheron S, Taieb A, et al. Long-term nonprogressors and elite controllers in the ANRS CO5 HIV-2 cohort. *AIDS*. 2011;25(6):865-867. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21358376>.
82. Menendez-Arias L, Alvarez M. Antiretroviral therapy and drug resistance in human immunodeficiency virus type 2 infection. *Antiviral Res*. 2014;102:70-86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24345729>.
83. Tchounga BK, Inwoley A, Coffie PA, et al. Re-testing and misclassification of HIV-2 and HIV-1&2 dually reactive patients among the HIV-2 cohort of the West African database to evaluate AIDS collaboration. *J Int AIDS Soc*. 2014;17:19064. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25128907>.
84. Balestre E, Ekouevi DK, Tchounga B, et al. Immunologic response in treatment-naive HIV-2-infected patients: the IeDEA West Africa cohort. *J Int AIDS Soc*. 2016;19(1):20044. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26861115>.
85. Linley L, Ethridge SF, Oraka E, et al. Evaluation of supplemental testing with the multispot HIV-1/HIV-2 rapid test and APTIMA HIV-1 RNA qualitative assay to resolve specimens with indeterminate or negative HIV-1 Western blots. *J Clin Virol*. 2013;58 Suppl 1:e108-112. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24342469>.
86. Burgard M, Jasseron C, Matheron S, et al. Mother-to-child transmission of HIV-2 infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1. *Clin Infect Dis*. 2010;51(7):833-843. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20804413>.

# Clinical and Laboratory Monitoring of Pediatric HIV Infection

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## Panel's Recommendations

- Absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of HIV diagnosis and, if a child is **not** started on antiretroviral therapy (ART) after diagnosis, this monitoring **should be repeated** at least every 3 to 4 months thereafter (**AIII**).
- Absolute CD4 count is recommended for monitoring immune status in children of all ages, with CD4 percentage as an alternative for children aged <5 years (**AII**).
- Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all ART-naïve patients (**AII**). Genotypic resistance testing is preferred for this purpose (**AIII**).
- After initiation of ART, or after a change in ARV regimen, children should be evaluated for clinical adverse effects and should receive support for treatment adherence within 1 to 2 weeks; laboratory testing for toxicity and viral load response is recommended at 2 to 4 weeks after treatment initiation (**AIII**).
- Children on ART should be monitored for therapy adherence, effectiveness, and toxicities routinely (every 3–4 months) (**AII\***).
- Additional CD4 count and plasma viral load monitoring should be performed to evaluate children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value (**AIII**). CD4 count can be monitored less frequently (every 6–12 months) in children and adolescents who are adherent to therapy, who have sustained virologic suppression and CD4 count values that are well above the threshold for opportunistic infection risk, and who have stable clinical status (**AII**). Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence and disease progression (**AIII**).
- Phenotypic resistance testing should be considered (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after a patient has experienced virologic failure on multiple ARV regimens (**CIII**).
- 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 ARV 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 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 counts and plasma viral loads measured, and their growth and development should be evaluated for signs of HIV-associated abnormalities. Testing should also be performed to assess for HIV-associated conditions, including anemia, leukopenia, thrombocytopenia, hypoalbuminemia, nephropathy (urinalysis), hyperglycemia, hepatic transaminitis, and

renal insufficiency (creatinine). In addition, children with HIV should have a complete, age-appropriate medical history and physical examination (see Table 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 when available documentation is incomplete (see [Diagnosis of HIV Infection in Infants and Children](#)). Genotypic resistance testing should be performed, even if ART is not initiated immediately. In addition, a full antiretroviral (ARV) drug history should be obtained; this history should include any exposure to ARV drugs for the prevention of perinatal HIV transmission (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). If abacavir (ABC) is being considered as a component of the regimen, HLA-B\*5701 testing should be sent prior to initiating ABC, 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](#)).<sup>1</sup>

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 and/or their caregiver (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 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 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, and hepatic transaminases) should be performed. The levels of serum lipids (cholesterol and triglycerides) should also be measured. A CBC allows clinicians to monitor 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 levels (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 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 phone or e-health check-ins 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 Initiating 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 Initiating Antiretroviral Therapy**

Most experts recommend performing laboratory testing at 2 weeks to 4 weeks (but no later than 8 weeks) after initiating 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 that 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 (1–3 months), clinicians should assess a patient's adherence to the regimen and the regimen's effectiveness (as measured by CD4 count and plasma viral load) every 3 to 4 months. Additionally, clinicians should review a patient's history of 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 ARV regimen that a child is receiving.

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

Recent studies have critically evaluated the frequency of laboratory monitoring in both adults and children, particularly CD4 count and plasma viral load. These studies support less frequent monitoring in stable patients who have been consistently virologically suppressed for  $\geq 1$  year.<sup>3-9</sup>

The [Adult and Adolescent Antiretroviral Guidelines](#) currently support performing plasma viral load testing every 6 months for individuals who have both:

- Consistent virologic suppression  $\geq 2$  years; *and*
- CD4 counts that are consistently  $>300$  cells/mm<sup>3</sup>.

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV finds value in continuing to perform viral load testing every 3 to 4 months to provide enhanced monitoring of adherence or disease progression among children and adolescents. Some experts monitor CD4 count less frequently (e.g., every 6–12 months) in children and adolescents who are adherent to therapy, who have CD4 count values well above the threshold for OI risk, and who have had sustained virologic suppression and stable clinical status for  $>2$  to 3 years.<sup>10</sup> 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 Regimens***

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 the regimen is failing (see [Recognizing and Managing Antiretroviral](#)

[Treatment Failure](#)), resistance testing should be performed while a patient is still receiving the failing regimen. This optimizes the chance of identifying resistance mutations, because resistant strains may revert to wild type within a few weeks of stopping ARV drugs (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). Clinicians should consider performing phenotypic resistance testing, including co-receptor tropism testing, in addition to genotypic viral resistance testing in children who have experienced prolonged or repeated periods of viral nonsuppression on multiple ARV regimens.<sup>11</sup>

## Immunologic Monitoring in Children: General Considerations

When interpreting CD4 counts and percentages in children, clinicians must consider age as a factor. CD4 count and percentage values in healthy infants without HIV are considerably higher than values observed in adults without HIV; these infant values slowly decline to adult values by age 5 years. An analysis from the HPPM Collaborative Study found that CD4 percentage provided little or no additional prognostic value compared with CD4 count regarding short-term disease progression in children aged <5 years; similar results were reported in a study of older children.<sup>12</sup> The current pediatric HIV disease classification is based on absolute CD4 count, which is the preferred assay for monitoring and estimating the risk for disease progression and OIs.<sup>13</sup>

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

Medical practice guidelines now recommend that all people with HIV receive ART, regardless of their CD4 count and clinical stage. However, CD4 counts are used to determine risk profiles that affect the urgency of recommendations for when to initiate therapy in an ART-naive child with HIV infection and when to assess the need for OI prophylaxis (see [When to Initiate Therapy in Antiretroviral-Naive Children](#)). A meta-analysis from the HPPM Collaborative Study generated plots that can be used to estimate the short-term risk of progression to AIDS or death in the absence of effective ART, according to age and the most recent CD4 percentage/absolute CD4 count or HIV RNA viral load measurement.<sup>14</sup>

CD4 counts and percentages can show considerable inpatient variation.<sup>15</sup> Mild intercurrent illness, the receipt of vaccinations, or exercise can produce a transient decrease in CD4 count and percentage; thus, CD4 count and percentage are best measured when patients are clinically stable. Clinical decisions, especially those regarding therapy changes, should be made in response to confirmed changes in CD4 count or percentage in conjunction with a confirmed viral load determination. The CD4 count or percentage and viral load measurement should be confirmed by performing these tests a second time at least 1 week after the first tests.

## HIV RNA Monitoring in Children: General Considerations

Quantitative HIV RNA assays measure the plasma concentration of HIV RNA as copies/mL. Without therapy, plasma viral load initially rises to peak level during the period of primary infection in adults and adolescents, and then it declines by as much as 2 to 3 log<sub>10</sub> copies to reach a stable lower level (the virologic set point) approximately 6 to 12 months after acute infection.<sup>16,17</sup> 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.<sup>18</sup>

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.<sup>19,20</sup> 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.<sup>21</sup> After the first year of life, plasma viral load slowly declined during the next few years.<sup>21–24</sup> Viral load during the first 12 to 24 months after birth showed an average decline of approximately 0.6 log<sub>10</sub> copies/mL per year, followed by an average decline of 0.3 log<sub>10</sub> copies/mL per year until age 4 to 5

years. This pattern probably reflects the lower efficiency of a developing immune system in containing viral replication, and possibly the rapid expansion of HIV-susceptible cells that occurs with somatic growth.<sup>25</sup>

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.<sup>23</sup> 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.<sup>20</sup> In both children and adults with HIV, CD4 count or percentage and plasma viral load are independent predictors of disease progression and mortality risk, and using the two markers together more accurately defines prognosis.<sup>23,24,26,27</sup>

### ***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](#)). Temporary viral load elevations (“blips”) that are between the level of detection and 200 copies/mL to 500 copies/mL often are detected in adults<sup>28</sup> 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](#). 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<sub>10</sub> copies/mL (a two-fold difference) or more.<sup>29,30</sup> 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.<sup>31-33</sup>

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.<sup>31,34-38</sup> It is particularly relevant for immigrant and adopted 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<sub>10</sub> copies/mL (a three-fold difference) in either direction during the course of a day or on different days.<sup>26,30</sup> 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<sub>10</sub> copies/mL (a five-fold difference) in infants aged <2 years and differences >0.5 log<sub>10</sub> copies/mL (a three-fold difference) in children aged ≥2 years should be considered reflective of plasma viral load changes that are biologically and clinically significant.

Generally, no change in ARV treatment should be made as a result of a change in plasma viral load unless the change is confirmed by a second measurement. 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.<sup>39,40</sup> In addition, some human genetic polymorphisms are associated with drug toxicity or adverse events (e.g., using HLA-B\*5701 testing to predict ABC hypersensitivity; for more information, see the [Abacavir](#) section in [Appendix A: Pediatric Antiretroviral Drug Information](#)).<sup>41</sup> Future clinical practice will likely 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**

Laboratory Testing	Entry Into Care <sup>a</sup>	Pre-Therapy <sup>b</sup>	ART Initiation <sup>c</sup>	Weeks 1–2 on Therapy	Weeks 2–4 on Therapy	Every 3–4 Months <sup>d</sup>	Every 6–12 Months <sup>e</sup>	Virologic Failure (Prior to Switching ARV Regimens)
Medical History and Physical Examination <sup>f</sup>	✓	✓	✓	✓	✓	✓		✓
Adherence Evaluation		✓	✓	✓	✓	✓		✓
CD4 Count	✓	✓	✓			✓		✓
Plasma Viral Load	✓	✓	✓		✓	✓		✓
Resistance Testing	✓							✓
CBC with Differential	✓	✓	✓		✓	✓		✓
Chemistries <sup>g</sup>	✓	✓	✓		✓	✓		✓
Lipid Panel	✓		✓				✓	
Random Plasma Glucose <sup>h</sup>			✓				✓	
Urinalysis	✓		✓				✓	
HBV Screening <sup>i</sup>		✓						✓
Pregnancy Test for Women of Childbearing Age <sup>j</sup>		✓						✓

<sup>a</sup> See text for details on recommended laboratory tests to perform.

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

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

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

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

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

<sup>g</sup> Chemistries refer to a comprehensive metabolic panel.

<sup>h</sup> Random plasma glucose is collected in a gray-top blood collection tube or other designated tube.

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

<sup>j</sup> 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:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; CBC = complete blood count; CD4 = CD4 T lymphocyte; FTC = emtricitabine; HBV = hepatitis B virus; OI = opportunistic infection; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

**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	Aptima HIV-1 Quant Assay
Method	Real-time RT-PCR	Real-time NASBA	Real-time RT-PCR	Real-time RT-PCR	Real-time TMA
Dynamic Range	40–10 <sup>7</sup> copies/mL	25–10 <sup>7</sup> copies/mL	20–10 <sup>7</sup> copies/mL	37–11×10 <sup>7</sup> copies/mL	30–10 <sup>7</sup> copies/mL
Specimen Volume <sup>a</sup>	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL	≥0.4 mL
Manufacturer	Abbott Laboratories	bioMérieux	Roche	Siemens	Hologic, Inc.

<sup>a</sup> Smaller volumes for children can be accommodated.

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

## References

- Jesson J, Dahourou DL, Renaud F, Penazzato M, Leroy V. Adverse events associated with abacavir use in HIV-infected children and adolescents: a systematic review and meta-analysis. *Lancet HIV*. 2016;3(2):e64-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26847228>.
- Krogstad P, Patel K, Karalius B, et al. Incomplete immune reconstitution despite virologic suppression in HIV-1 infected children and adolescents. *AIDS*. 2015;29(6):683-693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25849832>.
- Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23473847>.
- Buscher A, Mugavero M, Westfall AO, et al. The Association of clinical follow-up intervals in HIV-infected persons with viral suppression on subsequent viral suppression. *AIDS Patient Care STDS*. 2013;27(8):459-466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23886048>.
- Hyle EP, Sax PE, Walensky RP. Potential savings by reduced CD4 monitoring in stable patients with HIV receiving antiretroviral therapy. *JAMA Intern Med*. 2013;173(18):1746-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23978894>.
- Buclin T, Telenti A, Perera R, et al. Development and validation of decision rules to guide frequency of monitoring CD4 cell count in HIV-1 infection before starting antiretroviral therapy. *PLoS One*. 2011;6(4):e18578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21494630>.
- Gaur AH, Flynn PM, Bitar W, Liang H. Optimizing frequency of CD4 assays in the era of highly active antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2013;29(3):418-422. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23016543>.
- Gale HB, Gitterman SR, Hoffman HJ, et al. Is frequent CD4+ T-lymphocyte count monitoring necessary for persons with counts ≥300 cells/μL and HIV-1 suppression? *Clin Infect Dis*. 2013;56(9):1340-1343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23315315>.
- Davies MA, Ford N, Rabie H, et al. Reducing CD4 monitoring in children on antiretroviral therapy with virologic suppression. *Pediatr Infect Dis J*. 2015;34(12):1361-1364. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26379169>.
- Kosalaraksa P, Boettiger DC, Bunupuradah T, et al. Low risk of CD4 decline after immune recovery in human immunodeficiency virus-infected children with viral suppression. *J Pediatric Infect Dis Soc*. 2017;6(2):173-177. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27295973>.
- Agwu AL, Yao TJ, Eshleman SH, et al. Phenotypic co-receptor tropism in perinatally HIV-infected youth failing antiretroviral therapy. *Pediatr Infect Dis J*. 2016;35(7):777-81. Available at: <http://www.ncbi.nlm.nih.gov>

[pubmed/27078121](http://pubmed/27078121).

12. HIV Paediatric Prognostic Markers Collaborative Study, Boyd K, Dunn DT, et al. Discordance between CD4 cell count and CD4 cell percentage: implications for when to start antiretroviral therapy in HIV-1 infected children. *AIDS*. 2010;24(8):1213-1217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20386428>.
13. Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Recomm Rep*. 2014;63(RR-03):1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24717910>.
14. Dunn D, HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet*. 2003;362(9396):1605-1611. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14630440>.
15. Raszka WV Jr, Meyer GA, Waecker NJ, et al. Variability of serial absolute and percent CD4+ lymphocyte counts in healthy children born to human immunodeficiency virus 1-infected parents. Military pediatric HIV consortium. *Pediatr Infect Dis J*. 1994;13(1):70-72. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7909598>.
16. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. *JAMA*. 1995;274(7):554-558. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7629984>.
17. Katzenstein TL, Pedersen C, Nielsen C, Lundgren JD, Jakobsen PH, Gerstoft J. Longitudinal serum HIV RNA quantification: correlation to viral phenotype at seroconversion and clinical outcome. *AIDS*. 1996;10(2):167-173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8838704>.
18. Mellors JW, Kingsley LA, Rinaldo CR Jr, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med*. 1995;122(8):573-579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7887550>.
19. Abrams EJ, Weedon J, Steketee RW, et al. Association of human immunodeficiency virus (HIV) load early in life with disease progression among HIV-infected infants. New York City Perinatal HIV Transmission Collaborative Study Group. *J Infect Dis*. 1998;178(1):101-108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9652428>.
20. Palumbo PE, Kwok S, Waters S, et al. Viral measurement by polymerase chain reaction-based assays in human immunodeficiency virus-infected infants. *J Pediatr*. 1995;126(4):592-595. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7699539>.
21. Shearer WT, Quinn TC, LaRussa P, et al. Viral load and disease progression in infants infected with human immunodeficiency virus type 1. Women and infants transmission study group. *N Engl J Med*. 1997;336(19):1337-1342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9134873>.
22. McIntosh K, Shevitz A, Zaknun D, et al. Age- and time-related changes in extracellular viral load in children vertically infected by human immunodeficiency virus. *Pediatr Infect Dis J*. 1996;15(12):1087-1091. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8970217>.
23. Mofenson LM, Korelitz J, Meyer WA, 3rd, 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. National Institute of child health and human development intravenous immunoglobulin clinical trial study group. *J Infect Dis*. 1997;175(5):1029-1038. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9129063>.
24. Palumbo PE, Raskino C, Fiscus S, et al. Predictive value of quantitative plasma HIV RNA and CD4+ lymphocyte count in HIV-infected infants and children. *JAMA*. 1998;279(10):756-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9508151>.
25. Krogstad P, Uittenbogaart CH, Dickover R, Bryson YJ, Plaeger S, Garfinkel A. Primary HIV infection of infants: the effects of somatic growth on lymphocyte and virus dynamics. *Clin Immunol*. 1999;92(1):25-33. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10413650>.
26. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. *Ann Intern Med*. 1997;126(12):929-938. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9182469>.
27. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1

- infection. *Ann Intern Med.* 1997;126(12):946-954. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9182471>.
28. Grennan JT, Loutfy MR, Su D, et al. Magnitude of virologic blips is associated with a higher risk for virologic rebound in HIV-infected individuals: a recurrent events analysis. *J Infect Dis.* 2012;205(8):1230-1238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22438396>.
  29. Brambilla D, Leung S, Lew J, et al. Absolute copy number and relative change in determinations of human immunodeficiency virus type 1 RNA in plasma: effect of an external standard on kit comparisons. *J Clin Microbiol.* 1998;36(1):311-314. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9431977>.
  30. Raboud JM, Montaner JS, Conway B, et al. Variation in plasma RNA levels, CD4 cell counts, and p24 antigen levels in clinically stable men with human immunodeficiency virus infection. *J Infect Dis.* 1996;174(1):191-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8655993>.
  31. Bourlet T, Signori-Schmuck A, Roche L, et al. HIV-1 load comparison using four commercial real-time assays. *J Clin Microbiol.* 2011;49(1):292-297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21068276>.
  32. Yan CS, Hanafi I, Kelleher AD, et al. Lack of correlation between three commercial platforms for the evaluation of human immunodeficiency virus type 1 (HIV-1) viral load at the clinically critical lower limit of quantification. *J Clin Virol.* 2010;49(4):249-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20884287>.
  33. Jennings C, Harty B, Granger S, et al. Cross-platform analysis of HIV-1 RNA data generated by a multicenter assay validation study with wide geographic representation. *J Clin Microbiol.* 2012;50(8):2737-2747. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22692747>.
  34. Haas J, Geiss M, Bohler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus (HIV) type 1 in children infected with HIV strains of African origin. *J Infect Dis.* 1996;174(1):244-245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8656008>.
  35. Kline NE, Schwarzwald H, Kline MW. False negative DNA polymerase chain reaction in an infant with subtype C human immunodeficiency virus 1 infection. *Pediatr Infect Dis J.* 2002;21(9):885-886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12380591>.
  36. Zaman MM, Recco RA, Haag R. Infection with non-B subtype HIV type 1 complicates management of established infection in adult patients and diagnosis of infection in newborn infants. *Clin Infect Dis.* 2002;34(3):417-418. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11774090>.
  37. Luft LM, Gill MJ, Church DL. HIV-1 viral diversity and its implications for viral load testing: review of current platforms. *Int J Infect Dis.* 2011;15(10):e661-670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21767972>.
  38. Sire JM, Vray M, Merzouk M, et al. Comparative RNA quantification of HIV-1 group M and non-M with the roche cobas AmpliPrep/Cobas TaqMan HIV-1 v2.0 and abbot real-time HIV-1 PCR assays. *J Acquir Immune Defic Syndr.* 2011;56(3):239-243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21164353>.
  39. Bienczak A, Cook A, Wiesner L, et al. The impact of genetic polymorphisms on the pharmacokinetics of efavirenz in African children. *Br J Clin Pharmacol.* 2016;82(1):185-198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26991336>.
  40. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. *AIDS.* 2017;31(8):1129-1136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28323755>.
  41. Small CB, Margolis DA, Shaefer MS, Ross LL. HLA-B\*57:01 allele prevalence in HIV-infected North American subjects and the impact of allele testing on the incidence of abacavir-associated hypersensitivity reaction in HLA-B\*57:01-negative subjects. *BMC Infect Dis.* 2017;17(1):256. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28399804>.

# When to Initiate Therapy in Antiretroviral-Naive Children (Last updated April 14, 2020; last reviewed April 14, 2020)

## Panel's Recommendations

- Antiretroviral therapy (ART) should be initiated in all infants and children with HIV infection (AI for children aged <3 months, AI\* for older children).
- Rapid ART initiation (defined as initiating ART immediately or within days of diagnosis), accompanied by a discussion of the importance of adherence and provision of subsequent adherence support, is recommended for all children with HIV.
- If a child with HIV has not initiated ART, health care providers should closely monitor the virologic, immunologic, and clinical status at least every 3 to 4 months (AIII).

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

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

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

## Overview

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends initiating treatment for all children with HIV. This recommendation is consistent with treatment recommendations for adults with HIV, as well as European recommendations for children with HIV issued by Pediatric European Network for Treatment of AIDS Treatment Guidelines.<sup>1</sup> Multiple studies have shown a benefit to early antiretroviral therapy (ART) initiation. In children aged <1 year, the health and survival benefit of immediate ART initiation has been clearly demonstrated in the CHER trial.<sup>2</sup> In addition, 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 and 24 months.<sup>3</sup> Several studies have reported that treatment initiation within the first year of life is also associated with reduced size of viral reservoirs.<sup>4-9</sup> An observational study of more than 20,000 children aged 1 year to 16 years from 19 cohorts in Europe, Southern Africa, and West Africa found that immediate ART was associated with lower mortality and better growth in children aged <10 years when compared with ART that was delayed until CD4 T lymphocyte (CD4) cell count decreased to <350 cells/mm<sup>3</sup>.<sup>10</sup> 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.<sup>11-15</sup>

In addition to the health benefits of rapid treatment initiation, which is defined as therapy that is initiated immediately or within days of diagnosis, treatment initiation in young infants with HIV during the early stages of HIV infection may control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species.<sup>16</sup> Initiation of therapy at higher CD4 counts has been associated with the presence of fewer drug-resistance mutations at virologic failure in adults.<sup>17</sup> Early therapy also preserves immune function, preventing clinical disease progression.<sup>18-20</sup>

## Survival and Health Benefits Associated with Early Treatment Initiation

The CHER trial was a randomized clinical trial in South Africa that initiated triple-drug ART in asymptomatic infants aged 6 to 12 weeks with perinatally acquired HIV and normal CD4 percentages (>25%). Immediate initiation of ART resulted in a 75% reduction in early mortality among these infants, compared with delaying treatment until the infants met clinical or immune criteria.<sup>2</sup> Most of the infant deaths in the delayed treatment arm occurred during the first 6 months after study entry. Consistent with the CHER trial, data from a number of observational studies in the United States, Europe, and South Africa

demonstrated that infants who receive early treatment are less likely to progress to AIDS or death, and they also have improved growth compared to those who start therapy later.<sup>21-23</sup>

Older children with Centers for Disease Control and Prevention (CDC) Clinical Stage 3-defining opportunistic infections (OIs) (see [Revised Surveillance Case Definition for HIV Infection](#) and Table 6) are at high risk of disease progression and death. **In general, studies that evaluate later initiation of ART in children have a selection bias, because children with perinatal infection and rapidly progressing disease may have died prior to receiving an HIV diagnosis or ART; children who present later for ART initiation may be slower progressors with a better prognosis.** However, a general trend toward lower mortality and better growth with earlier ART initiation was reported in an evaluation of observational data from 20,756 ART-naive children aged 1 year to 16 years at enrollment from 19 cohorts in Europe, Southern Africa, and West Africa.<sup>10</sup> 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 counts decreased to <350 cells/mm<sup>3</sup>. The multicenter, open-label PREDICT trial randomized 300 children with HIV aged 1 year to 12 years at enrollment (median age 6.4 years) to immediately initiate ART or to defer treatment until their CD4 percentage was <15%; the study reported better height gain among children who started ART immediately.<sup>24</sup> Similarly, other studies have reported an association between younger age at initiation of therapy and more rapid growth reconstitution.<sup>22,25-27</sup> U.S. and international studies have reported an association between delayed ART initiation and delay of pubertal development and menarche.<sup>28-30</sup> **In a study of Zimbabwean children (median age 11 years), earlier ART initiation and improved nutrition were positively associated with improved lung function.**<sup>31</sup>

### ***Neurodevelopmental Benefits Associated with Early Treatment Initiation***

A CHER trial substudy found that infants who initiated treatment early had significantly better gross motor and neurodevelopmental profiles than those whose therapy was deferred.<sup>32</sup> In a study of 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 had better gross motor and language attainment than infants who did not meet the parameters for effective treatment response.<sup>33</sup> In this study, an effective response to treatment was defined as HIV RNA <1,000 copies/mL, CD4 percentages ≥25%, and weight-for-age z-scores ≥-2 at 9 months of age. **A study of South African infants with perinatal HIV infection who initiated treatment within 21 days of life (median 6 days) found that early neurodevelopmental scores for these infants were within the normal range.**<sup>34</sup>

### ***Immune Benefits Associated with Early Treatment Initiation***

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.<sup>20</sup> **In a small study in Botswana, infants who initiated ART within the first 7 days of life were found to have decreased immune activation, a more poly-functional HIV-1-specific CD8 cell response, and a markedly reduced HIV latent reservoir compared with infants who initiated ART later in the first year of life.**<sup>9</sup> Shiao 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 and 24 months.<sup>3</sup> Available data suggest that both children and adults who initiate treatment with a higher CD4 percentage or CD4 count have better immune recovery than patients who initiate with lower CD4 percentages or CD4 counts.<sup>26,35-37</sup> 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%.<sup>38</sup> Finally, earlier age at ART initiation results in higher rates of CD4:CD8 ratio normalization **and improved immunogenicity of childhood vaccines.**<sup>39-41</sup>

Early initiation of suppressive ART (i.e., in infants aged <6 months) results in a significant proportion of infants with HIV who fail to produce their own HIV-specific antibodies. These infants appear to be HIV

seronegative when tested; however, viral reservoirs remain, and viral rebound occurs if ART is stopped.<sup>42-46</sup>

### ***Viral Reservoirs and Viral Suppression with Early Treatment Initiation***

Several studies have reported that early treatment of infants with perinatally acquired HIV is also associated with reduced size of viral reservoirs.<sup>4-7,9,47</sup> Many studies that compared the size of viral reservoirs in children who initiated ART before age 12 weeks to those who initiated ART at  $\geq 12$  weeks to  $\leq 2$  years of age have found that viral reservoir size (as measured by peripheral blood mononuclear cell [PBMC] HIV DNA levels) after 1 year and 4 years of ART significantly correlated with the age at ART initiation and the age at viral control.<sup>48-50</sup> Kuhn et al. found that initiating ART at a younger age was associated with lower levels of PBMC-associated HIV DNA. Furthermore, the authors reported that 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  $\leq 55$  copies/ $10^6$  cells.<sup>4</sup> 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).<sup>51</sup> In addition, among 61 children with perinatally acquired HIV in PHACS who achieved viral suppression at ages of  $<1$  year versus ages between 1 and 5 years, the mean half-life of HIV DNA from the time of viral suppression was shorter in the early suppressors—5.9 years versus 18.8 years, respectively.<sup>52</sup>

These findings 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 with HIV, who are destined for life-long treatment. Furthermore, near-complete control of viral replication has been reported in infants who initiated treatment early and who had sustained control of plasma viremia.<sup>42,53</sup>

The report of a prolonged remission in a child with perinatally acquired HIV in Mississippi generated discussion about early initiation of ART as presumptive treatment in newborns at high risk of HIV acquisition. This newborn, born to a mother who did not receive antenatal or perinatal ART, was treated with a three-drug antiretroviral (ARV) regimen at age 30 hours **that was continued following diagnostic testing that confirmed HIV infection. ART was continued** through age 18 months, and 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.<sup>54,55</sup>

This experience has prompted increasing support for initiating treatment as soon as the diagnosis is made during the first weeks of life, **to limit reservoir formation and possibly facilitate ART-free remission.** Although there are a limited number of case reports of lengthy remissions in children with perinatally acquired HIV **who have undergone treatment interruption,** current ARV regimens have not been shown to eradicate HIV infection because HIV persists in CD4 cells and other long-lived cells.<sup>56-59</sup> For these reasons, the Panel **does not recommend** empiric treatment interruption.

Managing treatment in neonates with HIV is complex from both a medical and social perspective. Because of limited safety and pharmacokinetic (PK) data for ARV drugs in full-term infants aged  $<2$  weeks and preterm infants aged  $\leq 4$  weeks, drug and dose selection in this age group is challenging (see [What to Start](#) and [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#)).<sup>60,61</sup> Hepatic and renal function 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.<sup>62</sup> When drug concentrations are subtherapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, ARV drug resistance can develop rapidly, particularly in young infants, who experience high levels of viral replication. Frequent follow-up for dose optimization during periods of rapid growth is especially important when treating young infants. Furthermore, clinicians should continually assess a patient's adherence and address potential barriers to adherence during this time (see [Adherence to](#)

**Summary**

Multiple studies have reported that early treatment initiation is associated with immune, growth, and neurodevelopmental benefits. In addition, early treatment initiation may limit the formation of the viral reservoir. The Panel recommends rapid initiation of ART (defined as initiating ART immediately or within days of diagnosis) for all children who receive an HIV diagnosis. The urgency of rapid treatment initiation is especially critical for children aged <1 year, who carry the highest risk of rapid disease progression and mortality. However, it is worth noting that treatment of full-term infants aged ≤2 weeks and preterm infants is complex, due to the limited data on the PKs and appropriate dosing of ARV drugs in this age group; this is an area of active investigation (see [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#)).<sup>61</sup> An exception to rapid initiation is that ART should be deferred in patients with tuberculosis or cryptococcal meningitis until treatment for these OIs has been tolerated for at least 2 weeks; appropriate timing of ART initiation in these cases should be discussed with a pediatric HIV specialist.

While therapy is being initiated, it is important to assess and discuss issues associated with adherence with caregivers and, when developmentally appropriate, with children. Intensive follow-up during the first few weeks to months after treatment initiation is also recommended to support the child and caregiver. Medication adherence is the core requirement for successful virologic control. The Panel recognizes that achieving consistent adherence in children is often challenging.<sup>63,64</sup> Incomplete adherence leads to loss of viral control and the selection of drug resistance mutations, but forcibly administering ARV drugs to younger children may result in treatment aversion. The need for life-long therapy can also lead to treatment fatigue, which occurs among many children with perinatally acquired HIV during adolescence.<sup>65</sup>

The Panel believes the benefits of early ART initiation outweigh the potential risks and recommends rapid initiation of ART in all children regardless of clinical, immunologic, or virologic status. However, individual clinical and/or psychosocial factors may lead patients, caregivers, and providers to make a collaborative decision to defer therapy. When making the decision to defer therapy, medical factors (e.g., the opportunity to limit seeding of the viral reservoir in newborns, the child’s HIV disease stage [see Table 5], the presence of HIV-related signs and symptoms [see Table 6]) need to be balanced against any potential barriers to rapid treatment initiation. If therapy is deferred, the health care provider should closely monitor a child’s virologic, immunologic, and clinical status at least every 3 to 4 months (AIII) (see [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#)). Clinicians should initiate ART in children with HIV in whom treatment has been deferred when:

- HIV RNA levels increase,
- CD4 count or percentage values decline (e.g., approaching CDC Stage 2 or 3; see Table 5),
- The child develops new HIV-related clinical symptoms (see Table 6), or
- The ability of a caregiver and child to adhere to the prescribed regimen improves.

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

Stage <sup>a</sup>	Aged <1 Year		Aged 1 Year to <6 Years		Aged ≥6 Years	
	Cells/mm <sup>3</sup>	%	Cells/mm <sup>3</sup>	%	Cells/mm <sup>3</sup>	%
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

<sup>a</sup> The stage is based primarily on the CD4 count; the CD4 count takes precedence over the CD4 percentage, and the percentage is considered only when the count is missing. If a Stage 3-defining condition has been diagnosed (see Table 6), then the stage is 3 regardless of CD4 test results.

**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:** CD4 = CD4 T lymphocyte

**Table 6. HIV-Related Symptoms and Conditions** (page 1 of 2)

<b>Mildly Symptomatic</b>
<p>Children with two or more of the following conditions, but none of the conditions listed in the Moderately Symptomatic category, are considered mildly symptomatic:</p> <ul style="list-style-type: none"> <li>• Lymphadenopathy (lymph nodes are <math>\geq 0.5</math> cm at more than two sites and/or bilateral at one site)</li> <li>• Hepatomegaly</li> <li>• Splenomegaly</li> <li>• Dermatitis</li> <li>• Parotitis</li> <li>• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media</li> </ul>
<b>Moderately Symptomatic</b>
<ul style="list-style-type: none"> <li>• Anemia (hemoglobin <math>&lt; 8</math> g/dL [<math>&lt; 80</math> g/L]), neutropenia (white blood cell count <math>&lt; 1,000</math> per <math>\mu\text{L}</math> [<math>&lt; 1.0 \times 10^9</math> per L]), and/or thrombocytopenia (platelet count <math>&lt; 100 \times 10^3</math> per <math>\mu\text{L}</math> [<math>&lt; 100 \times 10^9</math> per L]) persisting for <math>\geq 30</math> days</li> <li>• Bacterial meningitis, pneumonia, or sepsis (single episode)</li> <li>• Candidiasis, oropharyngeal (thrush), persisting for <math>&gt; 2</math> months in children aged <math>&gt; 6</math> months</li> <li>• Cardiomyopathy</li> <li>• CMV infection, with onset before age 1 month</li> <li>• Diarrhea, recurrent or chronic</li> <li>• Hepatitis</li> <li>• HSV stomatitis, recurrent (more than two episodes within 1 year)</li> <li>• HSV bronchitis, pneumonitis, or esophagitis with onset before age 1 month</li> <li>• Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome</li> <li>• Leiomyosarcoma</li> <li>• Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex</li> <li>• Nephropathy</li> <li>• Nocardiosis</li> <li>• Persistent fever (lasting <math>&gt; 1</math> month)</li> <li>• Toxoplasmosis, onset before age 1 month</li> <li>• Varicella, disseminated (complicated chickenpox)</li> </ul>
<b>AIDS-Defining Conditions</b>
<ul style="list-style-type: none"> <li>• Bacterial infections, multiple or recurrent<sup>a</sup></li> <li>• Candidiasis of bronchi, trachea, or lungs</li> <li>• Candidiasis of esophagus</li> <li>• Cervical cancer, invasive</li> <li>• Coccidioidomycosis, disseminated or extrapulmonary</li> <li>• Cryptococcosis, extrapulmonary</li> <li>• Cryptosporidiosis, chronic intestinal (<math>&gt; 1</math> month duration)</li> <li>• CMV disease (other than liver, spleen, or lymph nodes), onset at age <math>&gt; 1</math> month</li> <li>• CMV retinitis (with loss of vision)</li> <li>• Encephalopathy attributed to HIV<sup>b</sup></li> <li>• HSV: chronic ulcers (<math>&gt; 1</math> month duration) or bronchitis, pneumonitis, or esophagitis (onset at age <math>&gt; 1</math> month)</li> <li>• Histoplasmosis, disseminated or extrapulmonary</li> <li>• Isosporiasis, chronic intestinal (<math>&gt; 1</math> month duration)</li> <li>• Kaposi sarcoma</li> <li>• Lymphoma, Burkitt (or equivalent term)</li> <li>• Lymphoma, immunoblastic (or equivalent term)</li> <li>• Lymphoma, primary, of brain</li> <li>• <i>Mycobacterium avium</i> complex or <i>Mycobacterium kansasii</i>, disseminated or extrapulmonary</li> </ul>

**Table 6. HIV-Related Symptoms and Conditions** (page 2 of 2)

<b>AIDS-Defining Conditions, continued</b>
<ul style="list-style-type: none"><li>• <i>Mycobacterium tuberculosis</i> of any site, pulmonary, disseminated, or extrapulmonary</li><li>• <i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary</li><li>• <i>Pneumocystis jirovecii</i> (previously known as <i>Pneumocystis carinii</i>) pneumonia</li><li>• Pneumonia, recurrent<sup>c</sup></li><li>• Progressive multifocal leukoencephalopathy</li><li>• Salmonella septicemia, recurrent</li><li>• Toxoplasmosis of brain, onset at age &gt;1 month</li><li>• Wasting syndrome attributed to HIV<sup>b</sup></li></ul>

<sup>a</sup> Only among children aged <6 years.

<sup>b</sup> 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).

<sup>c</sup> Only among adults, adolescents, and children aged ≥6 years.

**Key:** CMV = cytomegalovirus; HSV = herpes simplex virus

**Modified from:**

Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).

Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

## References

1. Foster C, Bamford A, Turkova A, et al. Paediatric European network for treatment of AIDS treatment guideline 2016 update: antiretroviral therapy recommended for all children living with HIV. *HIV Med*. 2017;18(2):133-134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27385585>.
2. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233-2244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19020325>.
3. Shiao S, Strehlau R, Technau KG, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. *AIDS*. 2017;31(3):355-364. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27828785>.
4. Kuhn L, Paximadis M, Da Costa Dias B, et al. Age at antiretroviral therapy initiation and cell-associated HIV-1 DNA levels in HIV-1-infected children. *PLoS One*. 2018;13(4):e0195514. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29649264>.
5. Massanella M, Ananworanich J, Leyre L, et al. ARV prophylaxis/ART initiation at birth limits the size of the reservoir in children. Abstract 135. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/arv-prophylaxisart-initiation-birth-limits-size-reservoir-children>.
6. Shapiro RL, Lichtenfeld M, Hughes MD, et al. Low HIV reservoir at 84 weeks in very early treated HIV-infected children in Botswana. Abstract 136. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/low-hiv-reservoir-84-weeks-very-early-treated-hiv-infected-children-botswana>.
7. Tagarro A, Chan M, Zangari P, et al. Early and highly suppressive antiretroviral therapy are main factors associated with

low viral reservoir in European perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2018;79(2):269-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30211778>.

8. Veldsman KA, Janse van Rensburg A, Isaacs S, et al. HIV-1 DNA decay is faster in children who initiate ART shortly after birth than later. *J Int AIDS Soc*. 2019;22(8):e25368. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31441231>.
9. Garcia-Broncano P, Maddali S, Einkauf KB, et al. Early antiretroviral therapy in neonates with HIV-1 infection restricts viral reservoir size and induces a distinct innate immune profile. *Sci Transl Med*. 2019;11(520). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31776292>.
10. Schomaker M, Leroy V, Wolfs T, et al. Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe. *Int J Epidemiol*. 2017;46(2):453-465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27342220>.
11. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: does it reduce the risk of cardiovascular disease? *Curr Opin HIV AIDS*. 2014;9(1):54-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24275676>.
12. Ghislain M, Bastard JP, Meyer L, et al. Late antiretroviral therapy (ART) initiation is associated with long-term persistence of systemic inflammation and metabolic abnormalities. *PLoS One*. 2015;10(12):e0144317. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26636578>.
13. Achhra AC, Mocroft A, Ross M, et al. Impact of early versus deferred antiretroviral therapy on estimated glomerular filtration rate in HIV-positive individuals in the START trial. *Int J Antimicrob Agents*. 2017;50(3):453-460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28668686>.
14. Lundgren JD, Borges AH, Neaton JD. Serious non-AIDS conditions in HIV: benefit of early ART. *Curr HIV/AIDS Rep*. 2018;15(2):162-171. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29504063>.
15. Dharan NJ, Neuhaus J, Rockstroh JK, et al. Benefit of early versus deferred antiretroviral therapy on progression of liver fibrosis among people with HIV in the START randomized trial. *Hepatology*. 2019;69(3):1135-1150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30298608>.
16. Persaud D, Ray SC, Kajdas J, et al. Slow human immunodeficiency virus type 1 evolution in viral reservoirs in infants treated with effective antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2007;23(3):381-390. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17411371>.
17. Palumbo PJ, Fogel JM, Hudelson SE, et al. HIV drug resistance in adults receiving early vs. delayed antiretroviral therapy: HPTN 052. *J Acquir Immune Defic Syndr*. 2018;77(5):484-491. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29293156>.
18. Rinaldi S, Pallikkuth S, Cameron M, et al. Impact of early antiretroviral therapy initiation on HIV-specific CD4 and CD8 T cell function in perinatally infected children. *J Immunol*. 2020;204(3):540-549. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31889024>.
19. Planchais C, Hocqueloux L, Ibanez C, et al. Early antiretroviral therapy preserves functional follicular helper T and HIV-specific B cells in the gut mucosa of HIV-1-infected individuals. *J Immunol*. 2018;200(10):3519-3529. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29632141>.
20. Azzoni L, Barbour R, Pappasavas E, et al. Early ART results in greater immune reconstitution benefits in HIV-infected infants: working with data missingness in a longitudinal dataset. *PLoS One*. 2015;10(12):e0145320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26671450>.
21. Goetghebuer T, Le Chenadec J, Haelterman E, et al. Short- and long-term immunological and virological outcome in HIV-infected infants according to the age at antiretroviral treatment initiation. *Clin Infect Dis*. 2012;54(6):878-881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22198788>.
22. Shiau S, Arpadi S, Strehlau R, et al. Initiation of antiretroviral therapy before 6 months of age is associated with faster growth recovery in South African children perinatally infected with human immunodeficiency virus. *J Pediatr*. 2013;162(6):1138-1145 e1132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23312691>.

23. Iyun V, Technau KG, Eley B, et al. Earlier antiretroviral therapy initiation and decreasing mortality among HIV-infected infants initiating antiretroviral therapy within 3 months of age in South Africa, 2006-2017. *Pediatr Infect Dis J*. 2020;39(2):127-133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31725119>.
24. Puthanakit T, Saphonn V, Ananworanich J, et al. Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial. *Lancet Infect Dis*. 2012;12(12):933-941. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23059199>.
25. McGrath CJ, Chung MH, Richardson BA, Benki-Nugent S, Warui D, John-Stewart GC. Younger age at HAART initiation is associated with more rapid growth reconstitution. *AIDS*. 2011;25(3):345-355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21102302>.
26. Simms V, Rylance S, Bandason T, et al. CD4+ cell count recovery following initiation of HIV antiretroviral therapy in older childhood and adolescence. *AIDS*. 2018;32(14):1977-1982. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29927784>.
27. Traisathit P, Urien S, Le Coeur S, et al. Impact of antiretroviral treatment on height evolution of HIV infected children. *BMC Pediatr*. 2019;19(1):287. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31421667>.
28. Szubert AJ, Musiime V, Bwakura-Dangarembizi M, et al. Pubertal development in HIV-infected African children on first-line antiretroviral therapy. *AIDS*. 2015;29(5):609-618. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25710288>.
29. Williams PL, Jesson J. Growth and pubertal development in HIV-infected adolescents. *Curr Opin HIV AIDS*. 2018;13(3):179-186. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29432228>.
30. Williams PL, Abzug MJ, Jacobson DL, et al. Pubertal onset in children with perinatal HIV infection in the era of combination antiretroviral treatment. *AIDS*. 2013;27(12):1959-1970. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24145244>.
31. Rylance S, Rylance J, McHugh G, et al. Effect of antiretroviral therapy on longitudinal lung function trends in older children and adolescents with HIV-infection. *PLoS One*. 2019;14(3):e0213556. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30897116>.
32. Laughton B, Cornell M, Grove D, et al. Early antiretroviral therapy improves neurodevelopmental outcomes in infants. *AIDS*. 2012;26(13):1685-1690. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22614886>.
33. Benki-Nugent S, Wamalwa D, Langat A, et al. Comparison of developmental milestone attainment in early treated HIV-infected infants versus HIV-unexposed infants: a prospective cohort study. *BMC Pediatr*. 2017;17(1):24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28095807>.
34. Laughton B, Naidoo S, Dobbels E, et al. Neurodevelopment at 11 months after starting antiretroviral therapy within 3 weeks of life. *South Afr J HIV Med*. 2019;20(1):1008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31745434>.
35. Picat MQ, Lewis J, Musiime V, et al. Predicting patterns of long-term CD4 reconstitution in HIV-infected children starting antiretroviral therapy in sub-Saharan Africa: a cohort-based modelling study. *PLoS Med*. 2013;10(10):e1001542. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24204216>.
36. Le T, Wright EJ, Smith DM, et al. Enhanced CD4+ T-cell recovery with earlier HIV-1 antiretroviral therapy. *N Engl J Med*. 2013;368(3):218-230. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23323898>.
37. Desmonde S, Dicko F, Koueta F, et al. Association between age at antiretroviral therapy initiation and 24-month immune response in West-African HIV-infected children. *AIDS*. 2014;28(11):1645-1655. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24804858>.
38. Patel K, Hernan MA, Williams PL, et al. Long-term effectiveness of highly active antiretroviral therapy on the survival of children and adolescents with HIV infection: a 10-year follow-up study. *Clin Infect Dis*. 2008;46(4):507-515. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18199042>.
39. Seers T, Vassallo P, Pollock K, Thornhill JP, Fidler S, Foster C. CD4:CD8 ratio in children with perinatally acquired HIV-1 infection. *HIV Med*. 2018;19(9):668-672. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30084150>.

40. Moonsamy S, Suchard M, Madhi SA. Effect of HIV-exposure and timing of anti-retroviral treatment on immunogenicity of trivalent live-attenuated polio vaccine in infants. *PLoS One*. 2019;14(4):e0215079. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31002702>.
41. Pensiero S, Cagigi A, Palma P, et al. Timing of HAART defines the integrity of memory B cells and the longevity of humoral responses in HIV-1 vertically-infected children. *Proc Natl Acad Sci USA*. 2009;106(19):7939-7944. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19416836>.
42. Ananworanich J, Puthanakit T, Suntarattiwong P, et al. Reduced markers of HIV persistence and restricted HIV-specific immune responses after early antiretroviral therapy in children. *AIDS*. 2014;28(7):1015-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24384692>.
43. Payne H, Mkhize N, Otwombe K, et al. Reactivity of routine HIV antibody tests in children who initiated antiretroviral therapy in early infancy as part of the children with HIV early antiretroviral therapy (CHER) trial: a retrospective analysis. *Lancet Infect Dis*. 2015;15(7):803-809. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26043884>.
44. Kuhn L, Schramm DB, Shiao S, et al. Young age at start of antiretroviral therapy and negative HIV antibody results in HIV-infected children when suppressed. *AIDS*. 2015;29(9):1053-1060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25870988>.
45. Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J*. 2015;34(3):e48-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25742088>.
46. Wamalwa D, Benki-Nugent S, Langat A, et al. Treatment interruption after 2-year antiretroviral treatment initiated during acute/early HIV in infancy. *AIDS*. 2016;30(15):2303-2313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27177316>.
47. Foster C, Pace M, Kaye S, et al. Early antiretroviral therapy reduces HIV DNA following perinatal HIV infection. *AIDS*. 2017;31(13):1847-1851. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28609403>.
48. McManus M, Mick E, Hudson R, et al. Early combination antiretroviral therapy limits exposure to HIV-1 replication and cell-associated HIV-1 DNA levels in infants. *PLoS One*. 2016;11(4):e0154391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27104621>.
49. Martinez-Bonet M, Puertas MC, Fortuny C, et al. Establishment and replenishment of the viral reservoir in perinatally HIV-1-infected children initiating very early antiretroviral therapy. *Clin Infect Dis*. 2015;61(7):1169-1178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26063721>.
50. van Zyl GU, Bedison MA, van Rensburg AJ, Laughton B, Cotton MF, Mellors JW. Early antiretroviral therapy in South African children reduces HIV-1-infected cells and cell-associated HIV-1 RNA in blood mononuclear cells. *J Infect Dis*. 2015;212(1):39-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25538273>.
51. Persaud D, Patel K, Karalius B, et al. Influence of age at virologic control on peripheral blood human immunodeficiency virus reservoir size and serostatus in perinatally infected adolescents. *JAMA Pediatr*. 2014;168(12):1138-1146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25286283>.
52. Uprety P, Patel K, Karalius B, et al. Human immunodeficiency virus type 1 DNA decay dynamics with early, long-term virologic control of perinatal infection. *Clin Infect Dis*. 2017;64(11):1471-1478. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28329153>.
53. Bitnun A, Samson L, Chun TW, et al. Early initiation of combination antiretroviral therapy in HIV-1-infected newborns can achieve sustained virologic suppression with low frequency of CD4+ T cells carrying HIV in peripheral blood. *Clin Infect Dis*. 2014;59(7):1012-1019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24917662>.
54. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013;369(19):1828-1835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24152233>.
55. Luzuriaga K, Gay H, Ziemniak C, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. *N Engl J Med*. 2015;372(8):786-788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25693029>.

56. Frange P, Faye A, Avettand-Fenoel V, et al. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. *Lancet HIV*. 2016;3(1):e49-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26762993>.
57. Violari A, Cotton MF, Kuhn L, et al. A child with perinatal HIV infection and long-term sustained virological control following antiretroviral treatment cessation. *Nat Commun*. 2019;10(1):412. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30679439>.
58. Shiau S, Abrams EJ, Arpadi SM, Kuhn L. Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission? *Lancet HIV*. 2018;5(5):e250-e258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29739699>.
59. Koofhethile CK, Moyo S, Kotokwe KP, et al. Undetectable proviral deoxyribonucleic acid in an adolescent perinatally infected with human immunodeficiency virus-1C and on long-term antiretroviral therapy resulted in viral rebound following antiretroviral therapy termination: a case report with implications for clinical care. *Medicine (Baltimore)*. 2019;98(47):e18014. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31764816>.
60. Cotton MF, Holgate S, Nelson A, Rabie H, Wedderburn C, Mirochnick M. The last and first frontier—emerging challenges for HIV treatment and prevention in the first week of life with emphasis on premature and low birth weight infants. *J Int AIDS Soc*. 2015;18(Suppl 6):20271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26639118>.
61. Clarke DF, Penazzato M, Capparelli E, et al. Prevention and treatment of HIV infection in neonates: evidence base for existing WHO dosing recommendations and implementation considerations. *Expert Rev Clin Pharmacol*. 2018;11(1):83-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29039686>.
62. Chadwick EG, Yogev R, Alvero CG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS*. 2011;25(5):643-649. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21297419>.
63. Hazra R, Siberry GK, Mofenson LM. Growing up with HIV: children, adolescents, and young adults with perinatally acquired HIV infection. *Annu Rev Med*. 2010;61:169-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19622036>.
64. Simoni JM, Montgomery A, Martin E, New M, Demas PA, Rana S. Adherence to antiretroviral therapy for pediatric HIV infection: a qualitative systematic review with recommendations for research and clinical management. *Pediatrics*. 2007;119(6):e1371-1383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17533177>.
65. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among U.S. youth with perinatally acquired HIV. *AIDS*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31274538>.

# What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated April 14, 2020; last reviewed April 14, 2020)

## 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

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

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

- *Preferred*: Drugs or drug combinations are designated as *Preferred* for use in treatment-naïve 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 appropriate drug exposure. Additional considerations are listed above.
- *Alternative*: Drugs or drug combinations are designated as *Alternative* for initial therapy when clinical trial data in children or adults show efficacy, but the drugs or drug combinations have disadvantages when compared with *Preferred* regimens. Drugs or drug combinations may be classified as *Alternative* for use in treatment-naïve children if they are less effective or durable than a *Preferred* regimen in adults or children; if there are specific toxicity, dosing, formulation, administration, or interaction concerns; or if there is limited experience with the use of these drugs or drug combinations in children.

## Factors to Consider When Selecting an Initial Regimen

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

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

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

Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have antiviral activity and efficacy against hepatitis B virus (HBV) and should be considered for use in children with HBV/HIV coinfection. For a comprehensive [review 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 drug-resistance testing, potential AEs, pill size, and dosing frequency. Adherence to a prescribed regimen is necessary; therefore, the preferences of the patient and caregivers 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 (NVP)-based regimen in infants and children aged 2 to 35 months, regardless of maternal or infant exposure to peripartum, single-dose NVP prophylaxis. In children with prior NVP exposure, 21.7% of children receiving the LPV/r-based regimen experienced death, virologic failure, or toxicity by Week 24 compared to 39.6% of children receiving the NVP-based regimen. For children with no prior NVP exposure, death, virologic failure, and toxicity occurred in 18.4% of children receiving the LPV/r-based regimen and 40.1% of children receiving the NVP-based regimen.<sup>1</sup>
- Those in the NVP group demonstrated greater, but not statistically significant, improvements in CD4 counts and growth parameters. However, improvements in CD4 counts were only maintained up to 1 year after initiation of ART.<sup>2</sup> Similar improved immune and growth parameters were reported in the NEVEREST study, where these parameters were compared in children who switched to a NVP-containing regimen and those who continued on a LPV/r-containing regimen after achieving virologic suppression.<sup>3</sup> Improvements in metabolic parameters have also been seen in children who switched from LPV/r to efavirenz (EFV) at or after 3 years of age.<sup>4</sup>
- PENPACT-1 (PENTA 9/PACTG 390) compared a PI-based regimen and a NNRTI-based regimen in treatment-naïve children aged 30 days to <18 years (the study did not dictate the use of specific NNRTIs or PIs). In the PI-based regimen group, 49% of children received LPV/r and 48% received nelfinavir; in the NNRTI-based regimen group, 61% of children received EFV and 38% received NVP. After 4 years of follow-up, 73% of children who were randomized to receive PI-based therapy and 70% who were randomized to receive NNRTI-based therapy remained on their initial ARV regimen. In both groups, 82% of children had viral loads <400 copies/mL.<sup>5</sup>
- The PROMOTE-pediatrics trial demonstrated comparable virologic efficacy among children who were randomized to receive either an NNRTI-based or a LPV/r-based ARV regimen.<sup>6</sup> Children were aged 2 months to <6 years and had no perinatal exposure to NVP. Selection of the NNRTI was based on age (children aged <3 years received NVP, and those aged >3 years primarily received EFV). The proportion of children with viral loads <400 copies/mL at 48 weeks was 80% in the LPV/r arm versus 76% in the NNRTI arm, a difference of 4% that was not statistically significant (95% confidence interval [CI], -9% to +17%).

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

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

- Children aged <14 days: NVP
- Children aged <14 days and weighing  $\geq 2$  kg: Raltegravir (RAL)
- Children aged  $\geq 14$  days to <3 years: LPV/r or RAL
- Children aged  $\geq 3$  years and
  - Weighing <25 kg: Atazanavir/ritonavir (ATV/r), twice-daily darunavir/ritonavir (DRV/r), or RAL
  - Weighing  $\geq 25$  kg: Dolutegravir (DTG)
  - Weighing  $\geq 25$  kg: Elvitegravir/cobicistat (EVG/c). Only the fixed-dose combination (FDC) tablet that contains elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/c/FTC/TAF) is recommended at this time.

- Adolescents aged  $\geq 12$  years and weighing  $\geq 25$  kg: Bictegravir (BIC). BIC is only available as a component of the FDC tablet bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).

Alternative regimens are shown in Table 7 below.

## Integrase Strand Transfer Inhibitor-Based Regimens

Four INSTIs—BIC, DTG, EVG, and RAL—are approved by the FDA for treating ARV-naive adults and children with HIV. INSTI-based regimens have quickly become the recommended regimens in adults because of their virologic efficacy, lack of drug interactions, and favorable toxicity profile. RAL is approved for the treatment of infants and children from birth onwards with weights of  $\geq 2$  kg. DTG is approved by the FDA for use in children weighing  $\geq 30$  kg. The FDC tablet BIC/FTC/TAF (Biktarvy) is approved by the FDA for use in children weighing  $\geq 25$  kg. EVG has been studied in adolescents in two FDC regimens and in combination with two NRTIs and ritonavir (RTV) boosting. BIC and DTG, the second-generation INSTIs, have higher barriers to resistance than the first-generation INSTIs RAL and EVG<sup>10,11</sup> and may have more activity against non-B subtypes of HIV.<sup>12,13</sup>

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

### *Bictegravir*

BIC is available only as part of an FDC tablet that contains BIC 50 mg/FTC 200 mg/TAF 25 mg and is marketed as Biktarvy. BIC/FTC/TAF was approved by the FDA in 2018 for use in adults and in 2019 for use in children or adolescents weighing  $\geq 25$  kg. Biktarvy is approved for use in patients who have no ARV treatment history, and it can also be used to replace the current ARV regimen in patients who have been virologically suppressed (viral load  $< 50$  copies/mL) on a stable ARV regimen with no history of treatment failure and no known substitutions associated with resistance to the individual components of the FDC tablet.

Biktarvy was administered to adolescents aged 12 years to  $< 18$  years and weighing  $\geq 35$  kg who had maintained viral loads  $< 50$  copies/mL for  $\geq 6$  months. The drug was well tolerated; all 24 participants in the study had viral loads  $< 50$  copies/mL at Week 24, and drug exposure in these adolescent patients was similar to the exposure observed in adults. Another study demonstrated the efficacy and tolerability of Biktarvy in children aged 6 years to  $< 12$  years who weighed  $\geq 25$  kg, although serum trough concentrations were more variable in this child cohort than in adolescent or adult cohorts.<sup>14,15</sup>

The two studies described above were combined and continued for 48 weeks, at which time 74 of 75 participants had viral loads  $< 50$  copies/mL.<sup>14</sup>

#### Recommendation:

- BIC/FTC/TAF is recommended as a *Preferred* INSTI-based regimen for adolescents aged  $\geq 12$  years and weighing  $\geq 25$  kg (**AI\***) and as an *Alternative* INSTI-based regimen for children aged  $\geq 6$  years and weighing  $\geq 25$  kg (**AI\***). The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.

### *Dolutegravir*

The FDA has approved DTG for use in children weighing  $\geq 30$  kg. The approval was supported by data from a study of 46 treatment-experienced (but INSTI-naive) adolescents<sup>9,16</sup> and 11 treatment-experienced (but INSTI-naive) children aged  $\geq 6$  years.<sup>17</sup> The World Health Organization (WHO) recommends using DTG in children weighing  $\geq 20$  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 DTG can be used in children weighing  $\geq 20$  kg (see the [Dolutegravir](#) section in [Appendix A: Pediatric Antiretroviral Drug Information](#));<sup>18</sup> DTG has a very favorable safety profile and can be given once daily to treat INSTI-naive patients. Studies of DTG are ongoing in children as young as 4 weeks of age.<sup>19</sup>

In a prospective surveillance study of birth outcomes among pregnant women on ART in Botswana, a small but significant increase in the risk of neural tube defects (NTDs) was observed among infants born to women who were receiving DTG at the time of conception.<sup>20-22</sup> Specific recommendations about the initiation and use of DTG in adults and adolescents of childbearing potential and in those who are pregnant or trying to conceive 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, Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D: Dolutegravir Counseling Guide for Health Care Providers](#)).

#### Recommendation:

- DTG plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for children and adolescents aged  $\geq 3$  years and weighing  $\geq 25$  kg (AI\*). The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and pediatric studies.<sup>7,9,23,24</sup>
- DTG plus a two-NRTI backbone is recommended as an *Alternative* INSTI-based regimen for children aged  $\geq 3$  years and weighing  $\geq 20$  kg to  $< 25$  kg (AI\*). Data are limited on the efficacy and safety of using DTG in this weight group, and DTG PKs vary more among children in this weight group than among those weighing  $\geq 25$  kg.
- In light of concerns about the potential increased risk of NTDs with the use of DTG, pediatric and adolescent care providers should discuss this risk with patients who are receiving or initiating DTG and their caregivers so they can make informed decisions about the use of DTG (see [Appendix D: Dolutegravir Counseling Guide for Health Care Providers](#) in the [Perinatal Guidelines](#)). Specific recommendations about the use of DTG in women of childbearing potential, pregnant women, and women who are trying to conceive are available in the [Adult and Adolescent Antiretroviral Guidelines](#) (see [Table 6b](#)) and in the [Perinatal Guidelines](#) (see [Teratogenicity and Recommendations for Use of Antiretroviral Drugs During Pregnancy](#)).

### ***Elvitegravir***

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

#### Recommendation:

- EVG/c/FTC/TAF is recommended as a *Preferred* INSTI-based regimen for children and adolescents weighing  $\geq 25$  kg who have creatinine clearance (CrCl)  $\geq 30$  mL/min (AI\*). The Panel bases this recommendation on the virologic potency and safety profile observed for this combination in adult and adolescent studies.<sup>25-30</sup>

### ***Raltegravir***

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

#### Recommendation:

- RAL plus a two-NRTI backbone is recommended as a *Preferred* INSTI-based regimen for infants and children from birth to age 3 years who weigh  $\geq 2$  kg and for children aged  $\geq 3$  years and weighing  $< 25$  kg.

(AI\*). It is an *Alternative* INSTI-based regimen for children aged  $\geq 3$  years and weighing  $\geq 25$  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.<sup>7,31-38</sup> The Panel acknowledges that data regarding the efficacy of this agent in those aged  $< 2$  years are currently very limited.<sup>39</sup>

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

## Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

EFV (for children aged  $\geq 3$  months), etravirine (ETR; for children aged  $\geq 6$  years), NVP (for children aged  $\geq 15$  days), and rilpivirine (RPV; for children aged  $\geq 12$  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 ETR, and cross-resistance to other NNRTIs is common. Rare, but serious and potentially life-threatening, skin and hepatic toxicity can occur with the use of all NNRTI drugs, but these AEs are most frequently observed in patients taking NVP, at least among adults with HIV. NNRTIs have the potential to interact with other drugs that are also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted-PI regimens. [Table 8](#) lists the advantages and disadvantages of using NNRTIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information for each drug.

### *Efavirenz*

Although EFV dosing recommendations are available for patients aged  $\geq 3$  months and weighing  $\geq 3.5$  kg, the Panel does not endorse the use of this drug in infants and children aged 3 months to 3 years because the PKs of EFV in very young patients can be highly variable.

#### Recommendation:

- EFV plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for initial treatment of HIV in children aged  $\geq 3$  years (AI\*). The Panel bases this recommendation on data from studies that evaluated the efficacy and tolerability of this drug in adults and children.<sup>23,31,40-58</sup>

### *Nevirapine*

There are extensive clinical and safety data for the use of NVP in children with HIV, and NVP has shown ARV efficacy when used as a component in a variety of combination regimens.<sup>1,5,6,59-63</sup> NVP 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 NVP 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 NVP doses that are necessary for treatment.

Early testing of infants allows HIV infection to be confirmed before 14 days of age. The Panel recommends the use of NVP as a *Preferred* NNRTI when a clinician plans to initiate treatment 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 NVP in infants aged  $< 14$  days. Additional considerations regarding the use of NVP in infants aged  $< 14$  days can be found in [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#).

#### Recommendation:

- NVP plus a two-NRTI backbone is recommended as a *Preferred* NNRTI-based regimen in infants

aged <14 days and an *Alternative* NNRTI-based regimen for children aged  $\geq 14$  days to <3 years (**AI**). Clinicians should consider switching from NVP to LPV/r or RAL in children aged  $\geq 14$  days to <3 years, as these drugs are the *Preferred* ARV agents for this age bracket. LPV/r has better clinical outcomes than NVP in children aged <3 years. The Panel recommends switching from NVP to LPV/r in these patients, because NVP is associated with rare occurrences of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, and rare (but potentially life-threatening) instances of hepatitis. NVP also has a low barrier to resistance, and there is conflicting data about the virologic efficacy of NVP-based regimens compared to the efficacy of *Preferred* regimens.<sup>1,5,6,61-73</sup>

## Rilpivirine

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

### Recommendation:

- RPV plus a two-NRTI backbone is recommended as an *Alternative* NNRTI-based regimen for children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg who have HIV viral loads  $\leq 100,000$  copies/mL (**AI\***). The Panel bases this recommendation on the limited experience with RPV in adolescents and the larger body of evidence in adults.<sup>47,74-78</sup>

## 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-naïve children include virologic potency, dosing frequency, pill burden, food or fluid requirements, the availability of palatable pediatric formulations, the drug interaction profile, the toxicity profile (particularly toxicities related to metabolic complications), the age of the child, and the availability of data regarding the use of the drug in children. [Table 8](#) lists the advantages and disadvantages of using PIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.

RTV is a potent inhibitor of the CYP3A4 isoenzyme and can be used in low doses as a PK booster when coadministered with some PIs, increasing drug exposure by prolonging the half-life of the boosted PI. Currently, only LPV/r is available as a coformulated product. In addition, the use of RTV boosting increases the risk of hyperlipidemia<sup>79</sup> and drug interactions. **COBI is an alternative CYP3A4 inhibitor that can also be used as a booster. It is available in a single-drug tablet and in coformulations with ATV and with DRV. Currently, the single-drug tablet is approved by the FDA for administration with ATV in children weighing  $\geq 35$  kg and for administration with DRV in children weighing  $\geq 40$  kg.**

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

### *Atazanavir Boosted with Ritonavir or Cobicistat*

ATV is a once-daily PI that was approved by the FDA in March 2008 for use in combination with a two-NRTI backbone in children aged  $\geq 6$  years. ATV is most often boosted with RTV. Approval was extended in 2014 for use in infants and children aged  $\geq 3$  months and weighing  $\geq 5$  kg.<sup>80,81</sup> **ATV administered in combination with COBI has been approved by the FDA for use in adults and, using the single-agent COBI tablet, in children weighing  $\geq 35$  kg.**

### Recommendation:

- ATV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for children aged  $\geq 3$  years and weighing <25 kg. It is an *Alternative* PI-based regimen for children aged  $\geq 3$  months to <3

years and children aged  $\geq 3$  years and weighing  $\geq 25$  kg (AI\*). Atazanavir/cobicistat plus a two-NRTI backbone is an *Alternative* PI-based regimen for children weighing  $\geq 35$  kg. These regimens have been shown to be virologically potent in adult and pediatric studies and have been well tolerated in pediatric studies. However, the oral powder formulations of ATV and RTV and the oral solution formulation of RTV can be cumbersome to administer.<sup>34,43,76,79,82-88</sup>

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

### ***Darunavir Boosted with Ritonavir or Cobicistat***

DRV/r is approved by the FDA for use in ARV-naive and ARV-experienced children aged  $\geq 3$  years and weighing  $\geq 10$  kg. In addition, once-daily dosing of DRV/r is approved for ARV-naive children aged  $\geq 3$  years and weighing  $\geq 10$  kg, and for ARV-experienced patients who do not have DRV resistance-associated mutations. Once-daily dosing of DRV/r was investigated during a substudy of a twice-daily dosing trial in children aged 3 years to  $<12$  years. This PK evaluation lasted only 2 weeks, after which the participants switched back to the twice-daily regimen.<sup>89</sup> 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 ARV-naive and ARV-experienced children aged  $<12$  years, the Panel recommends a twice-daily dose of DRV/r in children aged  $>3$  years to  $<12$  years.<sup>90</sup> DRV administered in combination with COBI has been approved by the FDA for use in adults and, using the single-agent COBI tablet, in children weighing  $\geq 40$  kg.<sup>91</sup>

#### Recommendation:

- DRV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for children aged  $\geq 3$  years and weighing  $\geq 10$  kg but  $<25$  kg, and as an *Alternative* PI-based regimen for children aged  $\geq 3$  years and weighing  $\geq 25$  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 the development of drug resistance and excellent toxicity profile in adults and children.<sup>34,90,92-98</sup>
- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of an *Alternative* PI-based regimen in ARV-naive children and adolescents weighing  $\geq 40$  kg (AI\*).
- Twice-daily dosing of DRV/r should be used for children aged  $\geq 3$  years to  $<12$  years.
- Twice-daily dosing of DRV/r should be used when the following DRV resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- DRV/c plus a two-NRTI backbone is recommended as an *Alternative* PI-based regimen for adolescents aged  $\geq 12$  years and weighing  $\geq 40$  kg who are not sexually mature.

### ***Lopinavir/Ritonavir***

LPV/r is approved to treat HIV infection in infants and children with a postmenstrual age  $\geq 42$  weeks and postnatal age  $\geq 14$  days. Once-daily LPV/r dosing is approved by the FDA for initial therapy in adults,<sup>99</sup> but PK data in children do not support a recommendation for once-daily dosing.<sup>100-102</sup>

#### Recommendation:

- LPV/r plus a two-NRTI backbone is recommended as a *Preferred* PI-based regimen for infants with a postmenstrual age  $\geq 42$  weeks and postnatal age  $\geq 14$  days to  $<3$  years (AI) and as an *Alternative* PI-based regimen in children aged  $\geq 3$  years (AI\*). This regimen has been shown to be virologically potent in adult and pediatric studies and has been well tolerated in pediatric studies.<sup>23,45,82,83,92,99-101,103-107</sup>

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

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, eight NRTIs (zidovudine [ZDV], didanosine [ddI], 3TC, stavudine [d4T], abacavir [ABC], FTC, TDF, and TAF) are approved by the FDA for use in children aged <13 years. Dual-NRTI combinations that have been studied in children include:

- ZDV used in combination with ABC, ddI, or 3TC
- ABC used in combination with 3TC, d4T, or ddI
- FTC used in combination with d4T or ddI
- TDF used in combination with 3TC or FTC
- TAF used in combination with FTC<sup>29,53,84,108-112</sup>

The Panel **no longer recommends** using ddI or d4T 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 the different dual-NRTI backbone options that are recommended for initial therapy in children 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 backbones listed below, 3TC and FTC are interchangeable. Both 3TC and FTC are well tolerated and have few AEs. FTC is similar to 3TC and can be substituted for 3TC as one component of a preferred dual-NRTI backbone (i.e., FTC used in combination with ABC, TDF, or ZDV). The main advantage of FTC over 3TC is that it can be administered once-daily as part of an initial regimen. Both 3TC and FTC select for the M184V resistance mutation, which is associated with high-level resistance to both drugs, a modest decrease in susceptibility to ABC, and improved susceptibility to ZDV and TDF as a result of decreased viral fitness.<sup>113,114</sup>

### ***Dual-Nucleoside Reverse Transcriptase Inhibitor Backbones***

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

#### **Abacavir in Combination with Lamivudine or Emtricitabine**

ABC is approved for use in children aged  $\geq 3$  months when administered as part of an ARV regimen.

##### Recommendation:

- ABC plus 3TC or FTC is recommended as the *Preferred* dual-NRTI combination for children aged  $\geq 3$  months (**AI**). Studies of adults and children have reported virologic efficacy and favorable toxicity profiles for these combinations.<sup>32,115-122</sup>
- Once-daily dosing is recommended when using the pill formulation of ABC. Twice-daily dosing of liquid ABC is recommended for initial therapy; a change to once-daily dosing can be considered for clinically stable patients with undetectable viral loads and stable CD4 counts.<sup>123-126</sup>

#### **Tenofovir Alafenamide in Combination with Emtricitabine**

TAF is an oral prodrug of tenofovir. It is approved by the FDA as a component of an FDC tablet that also contains EVG, COBI, and FTC for the treatment of HIV in ARV-naive individuals weighing  $\geq 25$  kg who have an estimated CrCl  $\geq 30$  mL/min. Additional safety and PK data are available for children aged 6 years to <12 years who are receiving this FDC tablet.<sup>30</sup> An FDC tablet that contains FTC/TAF (Descovy) is also available.

### Recommendation:

- FTC/TAF is recommended as a *Preferred* dual-NRTI combination in children and adolescents weighing  $\geq 25$  kg who have estimated CrCl  $\geq 30$  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  $\geq 35$  kg who have estimated CrCl  $\geq 30$  mL/min (**AI\***). This combination is also recommended as a *Preferred* drug combination when used in the single-tablet regimen EVG/c/FTC/TAF for children and adolescents weighing  $\geq 25$  kg (**AI\***). The Panel makes these recommendations because TAF has a lower risk of renal and bone AEs than TDF.<sup>27,127</sup>
- FTC/TAF is neither approved by the FDA nor recommended for use in combination with a boosted PI in children weighing  $< 35$  kg, because this combination has not been adequately studied in this age and weight group.

### **Tenofovir Disoproxil Fumarate in Combination with Lamivudine or Emtricitabine**

TDF is approved by the FDA for use in children and adolescents aged  $\geq 2$  years when administered as part of an ARV regimen. Decreases in bone mineral density (BMD) have been observed in adults and children receiving TDF, but the clinical significance of these decreases is unknown.<sup>109-112,128,129</sup> Before starting treatment, clinicians should consider whether the benefits of using TDF outweigh the potential risks of decreased BMD.<sup>130</sup>

### Recommendation:

- TDF plus 3TC or FTC is recommended as an *Alternative* dual-NRTI combination for children aged  $\geq 2$  years to 12 years (**AI\***). The Panel bases this recommendation on the virologic efficacy and ease of dosing of these combinations.<sup>109-112,116-119,131-136</sup>

### **Zidovudine in Combination with Abacavir**

In a European pediatric study, patients who received ZDV plus ABC had lower rates of viral suppression and a greater number of toxicities that lead to regimen modification than patients who received ABC plus 3TC.<sup>108,115</sup>

### Recommendation:

- ZDV plus ABC is recommended as an *Alternative* dual-NRTI combination for children aged  $\geq 3$  months (**BII**).

### **Zidovudine in Combination with Lamivudine or Emtricitabine**

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

### Recommendation:

- ZDV plus 3TC or FTC is recommended as a *Preferred* dual-NRTI combination for infants and children from birth to age  $\leq 6$  years, and an *Alternative* combination in children aged  $\geq 6$  years and adolescents (**AI\***). However, twice-daily dosing is required for ZDV in children aged  $\geq 6$  years. Other NRTIs that only require once-daily dosing in children aged  $\geq 6$  years are available.<sup>120,137-139</sup>
- ZDV plus ABC is recommended as an *Alternative* dual-NRTI combination for use in children aged  $\geq 3$  months (**BII**). In children aged  $\geq 6$  years and adolescents who are not sexually mature (i.e., those with SMRs of 1–3), the Panel recommends ZDV plus 3TC or FTC as an *Alternative* dual-NRTI combination (**BII**).

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

		Patient Age and Weight Class				
		Birth to <14 Days of Age <sup>a,b,c</sup>	Children Aged ≥14 Days to <3 Years	Children Aged ≥3 Years and Weighing <25 kg	Children Aged ≥3 Years and Weighing ≥25 kg	Adolescents Aged ≥12 Years and Weighing ≥25 kg
INSTI-Based Regimens		Two NRTIs plus RAL <sup>c</sup>				
					Two NRTIs plus BIC <sup>d</sup>	
					Two NRTIs plus DTG <sup>e</sup>	
					Two NRTIs plus EVG/COBI <sup>f</sup>	
NNRTI-Based Regimens	Two NRTIs plus NVP <sup>a,g</sup>					
PI-Based Regimens		Two NRTIs plus LPV/r <sup>b</sup>				
				Two NRTIs plus ATV/r		
				Two NRTIs plus DRV/r <sup>h</sup>		

<sup>a</sup> If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are *Preferred* agents because they are the only options with dosing information available for this age group. 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 [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#). Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother’s last menstrual period and birth, plus the time elapsed after birth); LPV/r has produced better clinical outcomes 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.

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

<sup>c</sup> 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.

<sup>d</sup> BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF; this FDC tablet is recommended as a *Preferred* regimen for adolescents aged ≥12 years and weighing ≥25 kg. It is recommended as an *Alternative* regimen for children aged ≥6 years and weighing ≥25 kg.

<sup>e</sup> DTG is recommended as a *Preferred* agent only for children and adolescents aged ≥3 years and weighing ≥25 kg. It is recommended as an *Alternative* agent in children aged ≥3 years and weighing 20 kg to <25 kg. For children weighing <20 kg, the use of RAL can be considered when an INSTI-based regimen is desired.

<sup>f</sup> EVG is currently recommended only as a component of FDC tablets. Tablets containing EVG/c/FTC/TAF are recommended as a *Preferred* regimen for children and adolescents weighing ≥25 kg.

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

<sup>h</sup> 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, because there are other drugs that can be administered once daily. This combination is considered a *Preferred* option for adolescents aged ≥12 years with SMRs of 1–3 when once-daily administration is possible.

**Key:** ART = antiretroviral therapy; ATV/r = atazanavir/ritonavir; BIC = bictegravir; 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 Initial Therapy for HIV Infection in Children**

An ARV regimen for treatment-naive children is generally made up of a two-NRTI backbone and either one NNRTI **or** one INSTI **or** one PI boosted with RTV or COBI. Regimens are designated *Preferred* 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 doses and formulations (see [Table 8](#) below).

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

<b>Preferred Regimens</b>			
<b>Age</b>	<b>Regimens</b>		<b>FDC Available</b> (see <a href="#">Appendix A, Table 1</a> )
<b>Infants, Birth to Age &lt;14 Days<sup>a,b</sup></b>	Two NRTIs <b>plus</b> NVP		No
	Weight ≥2 kg	Two NRTIs <b>plus</b> RAL <sup>c</sup>	No
<b>Children Aged ≥14 Days to &lt;3 Years</b>	Two NRTIs <b>plus</b> LPV/r <sup>b</sup>		No
	Weight ≥2 kg	Two NRTIs <b>plus</b> RAL <sup>c</sup>	No
<b>Children Aged ≥3 Years</b>	Weight <25 kg	Two NRTIs <b>plus</b> ATV/r	No
		Two NRTIs <b>plus</b> twice-daily DRV/r <sup>d</sup>	No
		Two NRTIs <b>plus</b> RAL <sup>c</sup>	No
	Weight ≥25 kg	Two NRTIs <b>plus</b> DTG <sup>e</sup>	Yes
		Two NRTIs <b>plus</b> EVG/c <sup>f</sup>	Yes
<b>Adolescents Aged ≥12 Years with SMRs of 1–3</b>	Weight ≥25 kg	Two NRTIs <b>plus</b> BIC <sup>g</sup>	Yes
<b>Adolescents Aged ≥12 Years with SMRs of 4 or 5</b>	Refer to the <a href="#">Adult and Adolescent Antiretroviral Guidelines</a>		Yes
<b>Alternative Regimens</b>			
<b>Age</b>	<b>Regimens</b>		<b>FDC Available</b> (see <a href="#">Appendix A, Table 1</a> )
<b>Children Aged ≥14 Days to &lt;3 Years</b>	Two NRTIs <b>plus</b> NVP <sup>h</sup>		No
<b>Children Aged ≥3 Months to &lt;3 Years</b>	Two NRTIs <b>plus</b> ATV/r		No
<b>Children Aged ≥3 Years</b>	Weight ≥20 kg to <25 kg	Two NRTIs <b>plus</b> DTG <sup>e</sup>	No
<b>Children Aged ≥3 Years</b>	Weight ≥25 kg	Two NRTIs <b>plus</b> ATV/r	No
		Two NRTIs <b>plus</b> DRV/r <sup>d</sup>	No
		Two NRTIs <b>plus</b> RAL <sup>c</sup>	No
<b>Children Aged ≥3 Years</b>	Two NRTIs <b>plus</b> EFV <sup>i</sup>		No <sup>j</sup>
	Two NRTIs <b>plus</b> LPV/r		No
<b>Children Aged ≥6 Years to &lt;12 Years</b>	Weight ≥25 kg	Two NRTIs <b>plus</b> BIC <sup>g</sup>	Yes
<b>Adolescents Aged ≥12 Years with SMRs of 1–3</b>	Weight ≥35 kg	Two NRTIs <b>plus</b> RPV <sup>k</sup>	Yes
		Two NRTIs <b>plus</b> ATV/c	No <sup>j</sup>
	Weight ≥40 kg	Two NRTIs <b>plus</b> DRV/c <sup>l</sup>	Yes
<b>Adolescents Aged ≥12 Years with SMRs of 4 or 5</b>	Refer to the <a href="#">Adult and Adolescent Antiretroviral Guidelines</a>		Yes
<b>Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs</b>			
<b>Age</b>	<b>Dual-NRTI Backbone Options</b>		<b>FDC Available</b>
<b>Children, Birth to Age &lt;3 Months</b>	ZDV <b>plus</b> (3TC <b>or</b> FTC) <sup>m</sup>		No <sup>j</sup>

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

Preferred Dual-NRTI Backbone Options for Use in Combination with Other Drugs, continued		
Age	Dual-NRTI Backbone Options	FDC Available
Children Aged ≥3 Months to <6 Years	ABC <b>plus</b> (3TC <sup>n</sup> <b>or</b> FTC)	Yes
	ZDV <b>plus</b> (3TC <sup>m</sup> <b>or</b> FTC)	Yes
Children and Adolescents Aged ≥6 Years with SMRs of 1–3	ABC <b>plus</b> (3TC <sup>n</sup> <b>or</b> FTC)	Yes
	Weighing ≥25 kg and receiving a regimen that contains an INSTI or an NNRTI	FTC/TAF <sup>o</sup> Yes
Adolescents Aged ≥12 Years with SMRs of 4 or 5	Refer to the <a href="#">Adult and Adolescent Antiretroviral Guidelines</a>	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 <b>plus</b> ABC	No
Children Aged ≥2 Years to 12 Years	TDF <b>plus</b> (3TC <b>or</b> FTC) <sup>p</sup>	Yes
Children and Adolescents Aged ≥6 Years and SMRs of 1–3	ZDV <b>plus</b> (3TC <b>or</b> FTC) <sup>m</sup>	Yes

<sup>a</sup> If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are *Preferred* agents because they are the only options with dosing information available for this age group. 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 [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#). Switching from NVP to LPV/r should be considered when the infant is aged ≥14 days with a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth); LPV/r has produced better clinical outcomes 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.

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

<sup>c</sup> RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children from birth to age 2 years. No dosing information is available for preterm infants or those weighing <2 kg at birth.

<sup>d</sup> 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).

<sup>e</sup> DTG is recommended as a *Preferred* agent for children and adolescents aged ≥3 years and weighing ≥25 kg. It is recommended as an *Alternative* agent in children aged ≥3 years and weighing 20 kg to <25 kg. An FDC tablet that contains ABC/DTG/3TC (Triumeq) is available for children weighing ≥25 kg.

<sup>f</sup> EVG is currently recommended only as a component of FDC tablets. Tablets that contain EVG/c/FTC/TAF (Genvoya) are recommended as a *Preferred* regimen for children and adolescents weighing ≥25 kg.

<sup>g</sup> BIC is available only as part of an FDC tablet that contains BIC/FTC/TAF (Biktarvy); this FDC tablet is recommended as a *Preferred* regimen for adolescents aged ≥12 years and weighing ≥25 kg. It is recommended as an *Alternative* regimen for children aged ≥6 years and weighing ≥25 kg.

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

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

<sup>j</sup> FDA-approved FDC tablets are not included in this table when they are not approved for use in the specific patient populations being discussed.

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

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

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

<sup>m</sup> An FDC tablet that contains 3TC/ZDV (Combivir and generic) is available for use in children weighing  $\geq 30$  kg.

<sup>n</sup> An FDC tablet that contains ABC/3TC (Epzicom and generic) is available for use in children weighing  $\geq 25$  kg.

<sup>o</sup> FTC plus TAF is recommended as a *Preferred* combination for children and adolescents weighing  $\geq 25$  kg; an FDC tablet that contains FTC/TAF (Descovy) is available. FTC/TAF is approved by the FDA for children weighing  $\geq 25$  kg when used in the single-tablet regimen EVG/c/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  $\geq 35$  kg.

<sup>p</sup> An FDC tablet that contains FTC/TDF (Truvada) is available.

**Key:** 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; **ATV/c = atazanavir/cobicistat**; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte; COBI = cobicistat; DRV = darunavir; **DRV/c = darunavir/cobicistat**; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; 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; the Panel = the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (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	<b>INSTI Class Advantages:</b> <ul style="list-style-type: none"> <li>• Few drug-drug interactions</li> <li>• Well-tolerated</li> </ul>	<b>INSTI Class Disadvantages:</b> <ul style="list-style-type: none"> <li>• Limited data on pediatric dosing or safety</li> </ul>
	BIC	Once-daily administration Can give with or without food Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> )	The FDC tablet <b>is not recommended</b> for patients with hepatic impairment or an estimated CrCl $< 30$ mL/min. The FDC tablet <b>should not be coadministered</b> with rifampin or dofetilide.
	DTG	Once-daily administration Can give with food Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> ) Single-agent DTG pills are available in several doses 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 NTDs in infants born to women who were receiving DTG at the time of conception
	EVG	Once-daily administration Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> )	Among INSTIs, EVG has the lowest barrier to the development of resistance. If EVG is coadministered 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.

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children (page 2 of 4)**

ARV Class	ARV Agent(s)	Advantages	Disadvantages
<b>INSTIs</b> In Alphabetical Order, continued	RAL	Can give with food Available in tablet, chewable tablet, and powder formulations Once-daily administration (with RAL HD) can be used for treatment-naïve or virologically suppressed children weighing $\geq 40$ 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.
<b>NNRTIs</b> In Alphabetical Order	All NNRTIs	<b>NNRTI Class Advantages:</b> <ul style="list-style-type: none"> <li>• Long half-life</li> <li>• Lower risk of dyslipidemia and fat maldistribution than PIs</li> <li>• PI-sparing</li> <li>• Lower pill burden than PIs for children taking the solid formulation; easier to use and adhere to than PI-based regimens</li> </ul>	<b>NNRTI Class Disadvantages:</b> <ul style="list-style-type: none"> <li>• A single mutation can confer resistance, with cross-resistance between EFV and NVP.</li> <li>• 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.</li> <li>• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)</li> </ul>
	EFV	Once-daily administration Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> ) Potent ARV activity Can give with food (but avoid high-fat meals) Capsules can be opened and added to food.	Neuropsychiatric AEs (bedtime dosing is recommended to reduce CNS effects) Rash (generally mild) No commercially available liquid formulation Limited data on dosing for children aged <3 years No data on dosing for children aged <3 months
	NVP	Liquid formulation is available. Dosing information for young infants is available. Can give with food Extended-release formulation 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 <sup>2</sup> Low barrier to resistance
	RPV	Once-daily dosing Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> )	Should not use in patients with viral loads >100,000 copies/mL Must be taken with a $\geq 500$ kcal meal at a consistent time each day; this may affect adherence. Low barrier to resistance
<b>PIs</b> In Alphabetical Order	All PIs	<b>PI Class Advantages:</b> <ul style="list-style-type: none"> <li>• NNRTI-sparing</li> <li>• Clinical, virologic, and immunologic efficacy are well-documented.</li> <li>• Resistance to PIs requires multiple mutations.</li> <li>• When combined with a dual-NRTI backbone, a regimen that contains a PI targets HIV at two steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.</li> </ul>	<b>PI Class Disadvantages:</b> <ul style="list-style-type: none"> <li>• Metabolic complications, including dyslipidemia, fat maldistribution, and insulin resistance</li> <li>• Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4)</li> <li>• Higher pill burden than NRTI-based or NNRTI-based regimens for patients taking solid formulations</li> <li>• Poor palatability of liquid preparations, which may affect adherence</li> <li>• Most PIs require RTV boosting, resulting in drug interactions that are associated with RTV</li> </ul>

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children** (page 3 of 4)

<b>ARV Class</b>	<b>ARV Agent(s)</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>PIs</b> In Alphabetical Order, continued	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 pre-existing 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 $\geq 12$ years  Liquid formulation is available.  DRV requires a boosting agent.  Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> )	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
	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 tolerated better when taken with meal or snack.	Poor palatability of liquid formulation (bitter taste).  Liquid formulation should be administered with food.  RTV is associated with a large number of drug interactions.  Should not be administered to neonates before a postmenstrual age of 42 weeks (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) and a postnatal age $\geq 14$ days  Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)
<b>Dual-NRTI Backbones</b> In Alphabetical Order	ABC <b>plus</b> (3TC <b>or</b> FTC)	Palatable liquid formulations  Can give with food  Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> )	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC.
	FTC/TAF for children aged $\geq 6$ 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 <a href="#">Appendix A, Table 1</a> )	Limited data on the safety and efficacy of this combination in children  Increased lipid levels

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order, continued	TDF <b>plus</b> (3TC <b>or</b> FTC) for adolescents with SMRs of 4 or 5	Once-daily dosing for TDF Resistance is slow to develop. Lower risk of mitochondrial toxicity than other NRTIs Can give with food Available as reduced-strength tablets and oral powder for use in younger children Available in FDC tablets (see <a href="#">Appendix A, Table 1</a> )	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 <b>plus</b> (3TC <b>or</b> FTC)	Extensive pediatric experience Coformulations of ZDV and 3TC are available (Combivir and generic) for children weighing ≥30 kg. Palatable liquid formulations Can give with food FTC is available as a palatable liquid formulation that can be administered once daily.	Bone marrow suppression and lipoatrophy with ZDV
	ZDV <b>plus</b> ABC	Palatable liquid formulations Can give with food	Risk of ABC HSR; perform HLA-B*5701 screening before initiating ABC. Bone marrow suppression and lipoatrophy with ZDV

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

## References

1. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. 2012;366(25):2380-2389. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716976>.
2. Barlow-Mosha L, Angelidou K, Lindsey J, et al. Nevirapine- versus lopinavir/ritonavir-based antiretroviral therapy in HIV-infected infants and young children: long-term follow-up of the IMPAACT P1060 randomized trial. *Clin Infect Dis*. 2016;63(8):1113-1121. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27439527>.
3. Coovadia A, Abrams EJ, Stehla R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA*. 2010;304(10):1082-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823434>.
4. Murnane PM, Stehla R, Shiao S, et al. Switching to efavirenz versus remaining on ritonavir-boosted lopinavir in HIV-infected children exposed to nevirapine: long-term outcomes of a randomized trial. *Clin Infect Dis*. 2017;65(3):477-485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28419200>.
5. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an

- open-label, randomised Phase 2/3 trial. *Lancet Infect Dis*. 2011;11(4):273-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21288774>.
6. Ruel TD, Kakuru A, Ikilezi G, et al. Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir/ritonavir or nonnucleoside reverse transcriptase inhibitor therapy. *J Acquir Immune Defic Syndr*. 2014;65(5):535-541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24326597>.
  7. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24074642>.
  8. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25393999>.
  9. Viani RM, Alvero C, Fenton T, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatr Infect Dis J*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26244832>.
  10. Tsiang M, Jones GS, Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. *Antimicrob Agents Chemother*. 2016;60(12):7086-7097. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27645238>.
  11. Hassounah SA, Alikhani A, Oliveira M, et al. Antiviral activity of bictegravir and cabotegravir against integrase inhibitor-resistant SIVmac239 and HIV-1. *Antimicrob Agents Chemother*. 2017;61(12). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28923862>.
  12. Neogi U, Singh K, Aralaguppe SG, et al. Ex-vivo antiretroviral potency of newer integrase strand transfer inhibitors cabotegravir and bictegravir in HIV type 1 non-B subtypes. *AIDS*. 2018;32(4):469-476. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29239896>.
  13. Oliveira M, Ibanescu RI, Anstett K, et al. Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir. *Retrovirology*. 2018;15(1):56. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30119633>.
  14. Gaur A, Cotton M, Rodriguez C, et al. Bictegravir/FTC/TAF single-tablet regimen in adolescents & children: Week 48 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <http://www.croiwebcasts.org/p/2019croi/46>
  15. Cotton M, Liberty A, Rodriguez CA, et al. Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in HIV-1-infected children (6 to < 12 years). Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_39.htm](http://www.natap.org/2018/IAC/IAC_39.htm).
  16. Wiznia A, Alvero C, Fenton T, et al. IMPAACT 1093: dolutegravir in 6- to 12-year-old HIV-infected children: 48-week results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, Massachusetts.
  17. Viani R, Carmelita A, Fenton T, et al. Safety, pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV+ children. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA.
  18. Bollen P, Turkova A, Mujuru H, et al. Adult dolutegravir 50 mg film-coated tablets in children living with HIV weighing 20 to < 25 kg. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.
  19. Ruel T, Acosta EP, Singh R, et al. Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSKI349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT PI093. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_44.htm](http://www.natap.org/2018/IAC/IAC_44.htm).
  20. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med*. 2018;379(10):979-981. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30037297>.

21. Zash R, Holmes L, Makhema J, et al. Surveillance for neural tube defects following antiretroviral exposure from conception. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_52.htm](http://www.natap.org/2018/IAC/IAC_52.htm).
22. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31329379>.
23. Walmsley S, Baumgarten A, Berenguer J, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naïve patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr*. 2015;70(5):515-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26262777>.
24. Viani RM, Ruel T, Alvero C, et al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: results of the IMPAACT P1093 Study. *J Pediatric Infect Dis Soc*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30951600>.
25. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65(3):e118-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24256630>.
26. Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs. ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr*. 2014;65(3):e121-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24346640>.
27. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25890673>.
28. Gaur A, Fourle J, et al. Pharmacokinetics, efficacy and safety of an integrase inhibitor STR in HIV-infected adolescents. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, Massachusetts.
29. Gaur AH, Kizito H, Prasitsuebsai W, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naïve, HIV-infected adolescents: a single-arm, open-label trial. *Lancet HIV*. 2016;3(12):e561-e568 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27765666>.
30. Gaur A, Natukunda E, Kosalaraksa P, et al. Pharmacokinetics, safety & efficacy of E/C/F/TAF in HIV-infected children (6-12 yrs). Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
31. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19647866>.
32. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clin Trials*. 2012;13(4):228-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22849964>.
33. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23412015>.
34. Lennox JL, Landovitz RJ, Ribaldo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25285539>.
35. Briz V, Leon-Leal JA, Palladino C, et al. Potent and sustained antiviral response of raltegravir-based highly active antiretroviral therapy in HIV type 1-infected children and adolescents. *Pediatr Infect Dis J*. 2012;31(3):273-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22330165>.
36. Nachman S, Zheng N, Acosta EP, et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-

infected children aged 2 through 18 years. *Clin Infect Dis*. 2014;58(3):413-422. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24145879>.

37. Nachman S, Alvero C, Acosta EP, et al. Pharmacokinetics and 48-week safety and efficacy of raltegravir for oral suspension in human immunodeficiency virus type-1-infected children 4 weeks to 2 years of age. *J Pediatric Infect Dis Soc*. 2015;4(4):e76-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26582887>.
38. Nachman S, Alvero C, Teppler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a Phase 1/2 open label, non-randomised, multicentre trial. *Lancet HIV*. 2018;5(12):e715-e722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30527329>.
39. Clarke D, Acosta A, Cababasay MP, et al. Raltegravir pharmacokinetics and safety in HIV-1 exposed neonates: dose-finding study. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
40. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-1881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10601506>.
41. Teglas JP, Quartier P, Treluyer JM, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. *AIDS*. 2001;15(2):241-243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11216933>.
42. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials*. 2002;3(3):186-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12032877>.
43. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr*. 2004;36(5):1011-1019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15247553>.
44. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: results from the Italian MASTER cohort. *J Antimicrob Chemother*. 2005;56(1):190-195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15917286>.
45. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18480202>.
46. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis*. 2010;201(6):803-813. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20151839>.
47. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the Phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr*. 2012;60(1):33-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22343174>.
48. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, Phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379(9835):2439-2448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22748591>.
49. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. 2000;182(6):1769-1773. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11069252>.
50. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(7):659-663. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12237599>.
51. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther*. 2004;9(2):297-299. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15134193>.

52. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res*. 2005;10(12):503-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16356864>.
53. McKinney RE Jr, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS clinical trials group protocol P1021. *Pediatrics*. 2007;120(2):e416-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17646352>.
54. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis*. 2005;41(11):1648-1653. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16267739>.
55. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*. 2001;15(1):71-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11192870>.
56. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS*. 2002;16(9):1201-1215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12045485>.
57. Zugar A. Studies disagree on frequency of late CNS side effects from efavirenz. *AIDS Clin Care*. 2006;4(1).
58. Kaul S, Ji P, Lu M, Nguyen KL, Shangguan T, Grasela D. Bioavailability in healthy adults of efavirenz capsule contents mixed with a small amount of food. *Am J Health Syst Pharm*. 2010;67(3):217-222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20101064>.
59. Bardsley-Elliott A, Perry CM. Nevirapine: a review of its use in the prevention and treatment of paediatric HIV infection. *Paediatr Drugs*. 2000;2(5):373-407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11022799>.
60. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. 1997;336(19):1343-1349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9134874>.
61. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. 2004;350(24):2471-2480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15190139>.
62. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS*. 2003;17(11):1639-1647. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12853746>.
63. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. 2010;363(16):1510-1520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20942667>.
64. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet*. 2004;363(9417):1253-1263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15094269>.
65. Soriano V, Arasteh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. *Antivir Ther*. 2011;16(3):339-348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21555816>.
66. Kanya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;46(2):187-193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17693883>.
67. Lowenthal ED, Ellenberg JH, Machine E, et al. Association between efavirenz-based compared with nevirapine-based antiretroviral regimens and virological failure in HIV-infected children. *JAMA*. 2013;309(17):1803-1809. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23632724>.
68. Kekitiinwa A, Spyer M, et al. Virologic response to efavirenz vs. nevirapine-containing ART in the ARROW trial. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, Massachusetts.
69. Baylor M, Ayime O, Truffa M, et al. Hepatotoxicity associated with nevirapine use in HIV-infected children. Presented at: Conference on Retroviruses and Opportunistic Infections. 2005. Boston, Massachusetts. Available at: <http://www>.

70. Buck WC, Kabue MM, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children. *J Int AIDS Soc*. 2010;13:31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20691049>.
71. Kea C, Puthanakit T, et al. Incidence and risk factors for nevirapine related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. Presented at: International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. 2011. Rome, Italy.
72. Mehta U, Maartens G. Is it safe to switch between efavirenz and nevirapine in the event of toxicity? *Lancet Infect Dis*. 2007;7(11):733-738. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17961859>.
73. Mbuagbaw L, Mursleen S, Irlam JH, Spaulding AB, Rutherford GW, Siegfried N. Efavirenz or nevirapine in three-drug combination therapy with two nucleoside or nucleotide-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naive individuals. *Cochrane Database Syst Rev*. 2016;12:CD004246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27943261>.
74. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a Phase 3, randomised, non-inferiority trial. *Lancet*. 2011;378(9787):229-237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21763935>.
75. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS*. 2013;27(6):939-950. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23211772>.
76. Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a Phase 3 randomised double-blind active-controlled trial. *Lancet*. 2011;378(9787):238-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21763936>.
77. Lombaard J, Bunupuradah T, Flynn PM, et al. Rilpivirine as a treatment for HIV-infected antiretroviral-naive adolescents: Week 48 safety, efficacy, virology and pharmacokinetics. *Pediatr Infect Dis J*. 2016;35(11):1215-1221 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27294305>.
78. Lombaard J, Bunupuradah T, et al. Safety and efficacy of a rilpivirine-based regimen in HIV-infected treatment-naive adolescents: Week 24 primary analysis of the PAINT Phase II trial. Presented at: International Workshop on HIV Pediatrics. 2014. Melbourne, Australia.
79. Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (A1424-097) 48-week results. *Clin Infect Dis*. 2007;44(11):1484-1492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17479947>.
80. Cotton MF, Liberty A, Torres-Escobar I, et al. Safety and efficacy of atazanavir powder and ritonavir in HIV-1-infected infants and children from 3 months to <11 years of age: the PRINCE-2 study. *Pediatr Infect Dis J*. 2018;37(6):e149-e156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29206747>.
81. Sevinsky H, Zaru L, Wang R, et al. Pharmacokinetics and pharmacodynamics of atazanavir in HIV-1-infected children treated with atazanavir powder and ritonavir: combined analysis of the PRINCE-1 and -2 Studies. *Pediatr Infect Dis J*. 2018;37(6):e157-e165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29206748>.
82. Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. *J Acquir Immune Defic Syndr*. 2008;47(2):161-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971713>.
83. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. 2010;53(3):323-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20032785>.
84. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil

fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2008;52(2):631-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025112>.

85. Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-1496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21610486>.
86. Rutstein RM, Samson P, Fenton T, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the pediatric AIDS clinical trials group protocol 1020A. *Pediatr Infect Dis J*. 2015;34:162-167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25232777>.
87. Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naïve and -experienced infants and children aged  $\geq 3$  months to  $< 6$  years. *J Int AIDS Soc*. 2015;18:19467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26066346>.
88. McFarland EJ, Heresi GP, Batra J, et al. Pharmacokinetics, safety, and efficacy of ATV or DRV with COBI in adolescents. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
89. Kakuda TN, Brochot A, van de Casteele T, Opsomer M, Tomaka F. Establishing darunavir dosing recommendations in treatment-naïve and treatment-experienced pediatric patients. Presented at: Clinical Pharmacology Workshop on HIV. 2013. Amsterdam, Netherlands. Available at: [http://www.natap.org/2013/Pharm/Pharm\\_19.htm](http://www.natap.org/2013/Pharm/Pharm_19.htm).
90. King J, Hazra R, et al. Pharmacokinetics of darunavir 800 mg with ritonavir 100 mg once daily in HIV+ adolescents and young adults. Presented at: Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, Georgia.
91. Food and Drug Administration. Tybost supplemental approval. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2019/203094Orig1s013ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/203094Orig1s013ltr.pdf)
92. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389-1397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18614861>.
93. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients: 96-week analysis. *AIDS*. 2009;23(13):1679-1688. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19487905>.
94. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label Phase 3b study. *Lancet*. 2014;383(9936):2222-2231. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24698485>.
95. Flynn P, Komar S, Blanche S, et al. Efficacy and safety of darunavir/ritonavir at 48 weeks in treatment-naïve, HIV-1-infected adolescents: results from a Phase 2 open-label trial (DIONE). *Pediatr Infect Dis J*. 2014;33(9):940-945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25361024>.
96. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS*. 2009;23(15):2005-2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19724191>.
97. Violari A, Bologna R, Kumarasamy N, et al. Safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients: week 48 results of the ARIEL trial. *Pediatr Infect Dis J*. 2015;34(5):e132-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25719453>.
98. Mascolini M. Darunavir dosing determined for naïve and experienced children and youth. Presented at: International Workshop on Clinical Pharmacology of HIV Therapy. 2013. Amsterdam, Netherlands.
99. Gathe J, da Silva BA, Cohen DE, et al. A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naïve subjects through 48 weeks. *J Acquir Immune Defic Syndr*. 2009;50(5):474-481. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19225400>.
100. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther*. 2008;13(8):1087-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19195335>.

101. la Porte C, van Heeswijk R, Mitchell CD, Zhang G, Parker J, Rongkavilit C. Pharmacokinetics and tolerability of once-versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther.* 2009;14(4):603-606. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19578247>.
102. Lyall H. Final results of Koncert: A randomized noninferiority trial of QD vs BD LPV/r dosing in children. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, Massachusetts.
103. Eron J Jr, Yeni P, Gathe J Jr, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet.* 2006;368(9534):476-482. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16890834>.
104. Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. *HIV Clin Trials.* 2009;10(2):76-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19487177>.
105. Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr.* 2009;50(4):367-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19214123>.
106. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med.* 2013;14(1):49-59. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23088336>.
107. Paediatric European Network for Treatment of AIDS. Once vs. twice-daily lopinavir/ritonavir in HIV-1-infected children. *AIDS.* 2015;29(18):2447-2457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26558544>.
108. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11888583>.
109. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics.* 2006;118(3):e711-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16923923>.
110. Giacomet V, Mora S, Martelli L, Merlo M, Sciannamblo M, Vigano A. A 12-month treatment with tenofovir does not impair bone mineral accrual in HIV-infected children. *J Acquir Immune Defic Syndr.* 2005;40(4):448-450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16280700>.
111. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):124-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14693529>.
112. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics.* 2005;116(6):e846-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16291735>.
113. Borroto-Esoda K, Vela JE, Myrick F, Ray AS, Miller MD. In vitro evaluation of the anti-HIV activity and metabolic interactions of tenofovir and emtricitabine. *Antivir Ther.* 2006;11(3):377-384. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16759055>.
114. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS.* 2004;18(12):1691-1696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15280780>.
115. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17457088>.
116. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med.* 2009;361(23):2230-2240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19952143>.

117. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23(12):1547-1556. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19542866>.
118. Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naive individuals. *Cochrane Database Syst Rev*. 2010(10):CD008740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20927777>.
119. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr*. 2010;55(1):49-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20431394>.
120. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis*. 2016;16(2):169-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26481928>.
121. Technau KG, Lazarus E, Kuhn L, et al. Poor early virologic performance and durability of abacavir-based first-line regimens for HIV-infected children. *Pediatr Infect Dis J*. 2013;32(8):851-855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23860481>.
122. Technau KG, Schomaker M, Kuhn L, et al. Virologic response in children treated with abacavir-compared with stavudine-based antiretroviral treatment: a South African multi-cohort analysis. *Pediatr Infect Dis J*. 2014;33(6):617-622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24378944>.
123. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther*. 2005;10(2):239-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15865218>.
124. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J*. 2006;25(6):533-537. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16732152>.
125. Paediatric European Network for Treatment of AIDS. Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-<36 months. *Antivir Ther*. 2010;15(3):297-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20516550>.
126. Musiime V, Kendall L, Bakeera-Kitaka S, et al. Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. *Antivir Ther*. 2010;15(8):1115-1124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21149918>.
127. Kizito H, Gaur A, Prasitsuebsai W, et al. Week-24 data from a Phase 3 clinical trial of E/C/F/TAF in HIV-infected adolescents. Presented at: Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, Washington.
128. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292(2):191-201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15249568>.
129. Vigano A, Bedogni G, Manfredini V, et al. Long-term renal safety of tenofovir disoproxil fumarate in vertically HIV-infected children, adolescents and young adults: a 60-month follow-up study. *Clin Drug Investig*. 2011;31(6):407-415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21528939>.
130. Giacomet V, Maruca K, Ambrosi A, Zuccotti GV, Mora S. A 10-year follow-up of bone mineral density in HIV-infected youths receiving tenofovir disoproxil fumarate. *Int J Antimicrob Agents*. 2017;50(3):365-370. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28689877>.
131. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354(3):251-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16421366>.
132. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with

zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr*. 2008;47(1):74-78. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971715>.

133. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J*. 2007;26(10):949-951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17901802>.
134. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United Kingdom and Ireland. *Pediatr Infect Dis J*. 2009;28(3):204-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19209091>.
135. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J*. 2009;28(7):619-625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19561425>.
136. Pontrelli G, Cotugno N, Amodio D, et al. Renal function in HIV-infected children and adolescents treated with tenofovir disoproxil fumarate and protease inhibitors. *BMC Infect Dis*. 2012;12:18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22269183>.
137. Van Dyke RB, Wang L, Williams PL, Pediatric AIDS Clinical Trials Group 219C Team. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. 2008;198(11):1599-1608. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19000014>.
138. Moyle GJ, Sabin CA, Cartledge J, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipodystrophy. *AIDS*. 2006;20(16):2043-2050. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17053350>.
139. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy: a randomized trial. *JAMA*. 2002;288(2):207-215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12095385>.

## What Not to Start: Regimens Not Recommended for Use in Antiretroviral-Naive Children (Last updated April 14, 2020; last reviewed April 14, 2020)

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 either 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 children for several years have been removed from this chapter, including the nucleoside reverse transcriptase inhibitors (NRTIs) stavudine and didanosine; the protease inhibitors (PIs) indinavir, nelfinavir, saquinavir, tipranavir (TPV), and fosamprenavir; and **the fusion inhibitor** enfuvirtide. Information about these agents is available in [Archived Drugs](#).

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

- **Not Recommended for Initial Therapy:** These include ARV drugs and drug combinations that are not recommended for initial therapy in ARV-naive children because they produce an inferior virologic response, they pose potential serious safety concerns (including potentially overlapping toxicities), they are associated with pharmacologic antagonism, or there are better options within a drug class. These drugs and drug combinations are listed in Table 9, **and selected drugs or drug combinations are discussed below.**
- **Insufficient Data to Recommend for Initial Therapy:** ARV drugs and drug combinations that are approved for use in adults but 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, **and selected drugs or drug combinations are discussed below.**
- **Antiretroviral Drug Regimens That Are *Never* Recommended:** Several ARV drug and drug combinations should never be used in children or adults. These are summarized in Table 10. Clinicians should also be aware of the components of fixed-dose combination (FDC) tablets so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

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

#### **Atazanavir without Ritonavir or Cobicistat Boosting**

Although unboosted atazanavir (ATV) is approved by the Food and Drug Administration (FDA) for use in treatment-naive adolescents aged  $\geq 13$  years and weighing  $\geq 40$  kg who are unable to tolerate ritonavir (RTV), data from the IMPAACT/PACTG 1020A study indicate that adolescents require higher doses of unboosted ATV (as measured by mg/m<sup>2</sup> of body surface area) than adults in order to achieve adequate drug concentrations.<sup>1</sup> The Panel **does not recommend** using ATV without RTV boosting because of these findings.

#### **Regimens that Contain Only Nucleoside Reverse Transcriptase Inhibitors**

In adult trials, regimens that contain only NRTIs have shown less potent virologic activity than non-nucleoside reverse transcriptase inhibitor (NNRTI)-based or PI-based regimens.<sup>2,3</sup> Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited to small observational studies.<sup>4,5</sup> In a study on the use of the triple-NRTI regimen abacavir plus lamivudine (3TC) plus zidovudine in ARV-experienced children, this combination showed evidence of only modest viral suppression; only 10 of the 102

children had viral loads of <400 copies/mL at Week 48 of treatment.<sup>6</sup> Therefore, regimens that contain only NRTIs **are not recommended** for treatment-naïve or treatment-experienced children.

### **Regimens that Contain Three Drug Classes**

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

### **Regimens that Contain Three Nucleoside Reverse Transcriptase Inhibitors and a Non-Nucleoside Reverse Transcriptase Inhibitor**

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.<sup>12</sup> 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 (**two NRTIs and one NNRTI**) or a four-drug regimen (three NRTIs and one NNRTI). After a 36-week induction period, the children on the four-drug regimen continued treatment on a regimen that contained **two** NRTIs plus **one** NNRTI or a three-NRTI regimen. Although improvements in CD4 T lymphocyte (CD4) cell counts were observed **at Week 36 (with a percentage change of approximately 14.4% in the four-drug arm compared to 12.6% in the three-drug arm)**, these benefits were not sustained after patients switched to the three-drug regimens **for the duration of the study. Furthermore, no differences in viral load suppression rates were observed between the two arms at Week 36.**<sup>13</sup> 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-naïve children or for specific age groups because of insufficient pediatric data. In some cases, new agents have shown promise in adult clinical trials but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. In addition, some dosing schedules may not be recommended in certain age groups 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.

### **Doravirine-Based Regimens**

Doravirine (DOR) is an NNRTI that is available as both a single-drug tablet and an FDC tablet that contains DOR 100 mg/3TC 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg and is marketed as Delstrigo. Efficacy studies in adults have demonstrated that DOR/3TC/TDF is noninferior to efavirenz (EFV)-based regimens and darunavir (DRV)-based regimens. DOR compared favorably to the other drugs in these trials in terms of adverse events. Currently, DOR is not approved for use in children or adolescents aged <18 years, but there are ongoing studies of DOR in children and adolescents. At this time, the Panel **does not recommend** the use of DOR in children or adolescents.

## **Darunavir with Low-Dose Ritonavir-Based Regimens Administered Once Daily for Children Aged $\geq 3$ Years to $< 12$ Years**

While modeling studies identified a once-daily dosing schedule for darunavir/ritonavir (DRV/r) that is now approved by the FDA, the Panel is concerned about the lack of direct PK studies for this approach in individuals aged  $\geq 3$  years to  $< 12$  years. Therefore, there is insufficient data to recommend once-daily dosing for initial therapy in this age group. For children aged  $\geq 3$  years to  $< 12$  years, twice-daily DRV/r is a *Preferred* drug combination. For older children who have undetectable viral loads while receiving a twice-daily DRV/r-based regimen, practitioners can consider switching to once-daily DRV/r dosing if no DRV-associated resistance mutations are present. Once-daily dosing helps support adherence by making this drug combination easier to use.

## **Efavirenz-Based Regimens for Children Aged $\geq 3$ Months to 3 Years**

EFV is approved by the FDA for use in children aged  $> 3$  months and weighing  $\geq 3.5$  kg. An EFV-based regimen has been shown to have variable PKs in studies of the very young; because of this, the Panel does not recommend using EFV in children aged  $< 3$  years at this time (see the [Efavirenz](#) section in [Appendix A: Pediatric Antiretroviral Drug Information](#)). When use of EFV 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 EFV. Therapeutic drug monitoring can also be considered.

## **Etravirine-Based Regimens**

Etravirine (ETR) is an NNRTI that has been studied in treatment-experienced children aged  $\geq 1$  years and is now approved by the FDA for use in children aged  $\geq 2$  years and weighing  $\geq 10$  kg.<sup>14-16</sup> It is associated with multiple interactions with other ARV drugs, including TPV/ritonavir, ATV/ritonavir, and unboosted PIs, and must be administered twice daily. It is unlikely that the use of ETR will be studied in treatment-naive children.

## **Maraviroc-Based Regimens**

Maraviroc (MVC) is an entry inhibitor that is approved by the FDA for use in children aged  $\geq 2$  years and weighing  $\geq 10$  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 MVC to treatment-experienced children aged 2 to 18 years who were divided into four age cohorts.<sup>17</sup> The initial dose was based on body surface area and scaled from the recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP3A4 inhibitor or inducer.<sup>18</sup> MVC 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.

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

ARV Regimen or Component	Rationale
Unboosted ATV-containing regimens in children	Reduced exposure
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing three drug classes	Potential to induce multiclass resistance Use as an initial regimen in children has not been studied
Regimens containing three NRTIs and one NNRTI	Added cost and complexity outweighs any benefit
Full-dose RTV or use of RTV as the sole PI	GI intolerance Metabolic toxicity
LPV/r dosed once daily	Reduced drug exposure
DOR-based regimens	Insufficient data to recommend
Once-daily DRV-based regimens in children aged $\geq 3$ years to <12 years	Insufficient data to recommend
EFV-based regimens for children aged <3 years	Appropriate dose not determined
ETR-based regimens	Insufficient data to recommend
MVC-based regimens	Insufficient data to recommend
Unboosted DRV	Use without RTV has not been studied
Full-dose, dual-PI regimens	Insufficient data to recommend Potential for added toxicities
TDF-containing regimens in children aged <2 years	Potential bone toxicity Appropriate dose has yet to be determined

**Key:** ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; DOR = doravirine; 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 Regimens or Components That Are Never Recommended for Treating HIV in Children**

<b>ARV Regimens That Are <u>Never</u> Recommended for Use in Children</b>		
<b>Regimen</b>	<b>Rationale</b>	<b>Exceptions</b>
<b>One ARV Drug Alone (Monotherapy)</b>	Rapid development of resistance Inferior antiviral activity compared to regimens that include $\geq 3$ ARV drugs Monotherapy “holding” regimens are associated with more rapid CD4 count declines than nonsuppressive ART.	Infants with perinatal HIV exposure and negative virologic tests who are receiving 4–6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV
<b>Two NRTIs Alone</b>	Rapid development of resistance Inferior antiviral activity compared to regimens that include $\geq 3$ ARV drugs	<b>Not recommended</b> for initial therapy Some clinicians may opt to continue using two NRTIs alone in patients who achieve virologic goals with this regimen.
<b>TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen</b>	High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults	<b>No exceptions</b>
<b>ARV Components That Are <u>Never</u> Recommended for Use as Part of an ARV Regimen for Children</b>		
<b>Regimen</b>	<b>Rationale</b>	<b>Exceptions</b>
<b>Dual-NNRTI Combinations</b>	Enhanced toxicity	<b>No exceptions</b>
<b>Dual-NRTI Combination of 3TC plus FTC</b>	Similar resistance profile and no additive benefit	<b>No exceptions</b>
<b>NVP as Initial Therapy in Adolescent Girls with CD4 Counts <math>&gt;250</math> cells/mm<sup>3</sup> or Adolescent Boys with CD4 Counts <math>&gt;400</math> cells/mm<sup>3</sup></b>	Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups	Only if benefit clearly outweighs risk

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

## References

1. Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-1496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21610486>.
2. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. *AIDS*. 2003;17(14):2045-2052. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14502007>.
3. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*. 2003;17(7):987-999. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12700448>.
4. Saavedra J, Mccoig C, Mallory M, et al. Clinical experience with triple nucleoside (NRTI) combination ZDV/3TC/abacavir (ABC) as initial therapy in HIV-infected children. Interscience Conference on Antimicrobial Agents and Chemotherapy. 2001. Chicago, Illinois.
5. Handforth J, Sharland M. Triple nucleoside reverse transcriptase inhibitor therapy in children. *Paediatr Drugs*. 2004;6(3):147-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15170362>.
6. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency

- virus type 1-infected children. The CNA3006 Study Team. *Pediatrics*. 2001;107(1):E4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11134468>.
7. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. 2000;182(6):1769-1773. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11069252>.
  8. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-1881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10601506>.
  9. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(7):659-663. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12237599>.
  10. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results of a randomized controlled trial—PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(12):1113-1121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10954886>.
  11. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
  12. Judd A, and EP, Paediatric HIV Cohort Collaboration study group in EuroCoord. Early antiretroviral therapy in HIV-1-infected infants, 1996–2008: treatment response and duration of first-line regimens. *AIDS*. 2011;25(18):2279-2287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21971357>.
  13. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23473847>.
  14. Konigs C, Feiterna-Sperling C, Esposito S, et al. Pharmacokinetics and short-term safety and tolerability of etravirine in treatment-experienced HIV-1-infected children and adolescents. *AIDS*. 2012;26(4):447-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22156961>.
  15. Tudor-Williams G, Cahn P, Chokephaibulkit K, et al. Etravirine in treatment-experienced, HIV-1-infected children and adolescents: 48-week safety, efficacy and resistance analysis of the Phase II PIANO study. *HIV Med*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24589294>.
  16. MacBrayne CE, Rutstein R, Yogev R, et al. Etravirine pharmacokinetics in treatment-experienced children ages 1- <6 years. Abstract 465. Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/etravirine-pharmacokinetics-treatment-experienced-children-ages-1-6>.
  17. Giaquinto C, Mawela MP, Chokephaibulkit K, et al. Pharmacokinetics, Safety and efficacy of maraviroc in treatment-experienced pediatric patients infected with CCR5-Tropic HIV-1. *Pediatr Infect Dis J*. 2018;37(5):459-465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29023357>.
  18. Vourvahis M. Update from Study A4001031: maraviroc pharmacokinetics in CCR5-tropic HIV-1-infected children aged 2 to < 18 years. IAS Conference on HIV Pathogenesis, Treatment and Prevention. 2013. Kuala Lumpur, Malaysia. Available at: <http://www.abstract-archive.org/Abstract/Share/13916>.

# Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection (Last Updated April 14, 2020; last reviewed April 14, 2020)

## Panel's Recommendations

- All newborns who were perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
- Newborn ARV regimens administered at doses that are appropriate for the infant's gestational age should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.
- A newborn's ARV regimen should be determined based on maternal and infant factors that influence the risk of perinatal transmission of HIV **(AII)**. The uses of ARV regimens in newborns include:
  - **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without documented HIV infection to reduce the risk of perinatal acquisition of HIV.
  - **Presumptive HIV Therapy:** The administration of a three-drug ARV regimen to newborns who are at highest risk of perinatal acquisition of HIV. Presumptive HIV therapy is intended to be preliminary treatment for a newborn who is later documented to have HIV, but it also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process, or during breastfeeding and who do not acquire HIV.
  - **HIV Therapy:** The administration of a three-drug ARV regimen at treatment doses (called antiretroviral therapy [ART]) to newborns with documented HIV infection (see [Diagnosis of HIV Infection in Infants and Children](#)).
- A 4-week zidovudine (ZDV) ARV prophylaxis regimen can be used in newborns whose mothers received ART during pregnancy and had sustained viral suppression near delivery (defined as a confirmed HIV RNA level <50 copies/mL) and for whom there are no concerns related to maternal adherence **(BII)**.
- Newborns at higher risk of perinatal acquisition of HIV should initiate presumptive HIV therapy (see Table 12 for recommended regimens). Newborns at higher risk of HIV acquisition 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 who did not achieve viral suppression near delivery **(AII)**, or
  - Have primary or acute HIV infection during pregnancy **(AII)**, or
  - Have primary or acute HIV infection while breastfeeding **(AII)**.
- Newborns of women with unknown HIV statuses who test HIV positive on expedited testing during labor or shortly after birth should initiate an ARV regimen (either presumptive HIV therapy or two-drug ARV prophylaxis, based on clinician assessment of risk) **(AII)**. If supplemental testing is negative, the ARV regimen should be discontinued **(AII)**.
- For newborns with HIV infection, ART should be initiated **(AI)**.
- The use of ARV drugs other than ZDV, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data **(BII)**.
- Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care **(AIII)**.

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

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

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

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

Maternal viral load is the most important risk factor for HIV transmission to a newborn. Newborns are at an increased risk of transmission when their mothers did not receive antiretroviral therapy (ART) during pregnancy, started antepartum treatment late in pregnancy, or when antepartum treatment did not result in virologic suppression. Higher maternal viral load, especially in late 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.

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 **presumptive** treatment of HIV. In this section, the following terms will be used:

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

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

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

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

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

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the [National Perinatal HIV Hotline](https://www.hivhotline.org/) (1-888-448-8765).

Level of Perinatal HIV Transmission Risk	Description	Neonatal ARV Management
<b>Low Risk of Perinatal HIV Transmission</b>	Mothers who received ART during pregnancy with sustained viral suppression (defined as a confirmed HIV RNA level <50 copies/mL) near delivery and no concerns related to adherence	ZDV for 4 weeks
<b>Higher Risk of Perinatal HIV Transmission<sup>a,b</sup></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 loads near delivery, particularly when delivery was vaginal Mothers with acute or primary HIV infection during pregnancy or breastfeeding (in which case, the mother <b>should discontinue breastfeeding</b> ) <sup>c</sup>	<b>Presumptive</b> HIV therapy using either ZDV, 3TC, and NVP (treatment dose) <i>or</i> ZDV, 3TC, and RAL administered from birth <b>up to</b> 6 weeks. <sup>d</sup>
<b>Presumed Newborn HIV Exposure</b>	Mothers with unconfirmed HIV status who have at least one positive HIV test at delivery or postpartum <i>or</i> Whose newborns have a positive HIV antibody test	ARV management as described above for newborns with a higher risk of perinatal HIV transmission  Infant ARV drugs should be discontinued immediately if supplemental testing confirms that the mother does not have HIV
<b>Newborn with HIV<sup>e</sup></b>	Positive newborn HIV virologic test/NAT	Three-drug ARV regimen using treatment doses

<sup>a</sup> See text for evidence that supports the use of **presumptive** HIV therapy and a two-drug ARV prophylaxis regimen.

<sup>b</sup> See [Intrapartum Care](#) 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.

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

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

<sup>e</sup> Most Panel members do not recommend delaying the initiation of ART pending results of the confirmatory HIV NAT, given the 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:** 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 3)**

<b>Newborns at Low Risk of Perinatal HIV Transmission</b>	
<b>Recommended Regimen</b>	<b>Recommended Duration</b>
ZDV	ZDV administered for 4 weeks <b>at the doses listed below</b>
<b>Newborns at Higher Risk of Perinatal HIV Transmission</b>	
<b>Recommended Regimen</b>	<b>Recommended Duration</b>
<b>Three-drug</b> HIV therapy: ZDV plus 3TC plus (NVP <i>or</i> RAL)	ZDV administered for 6 weeks, <b>with no increase to the 12 mg/kg dose unless the infant has confirmed HIV infection. Dosing for 3TC, NVP, and RAL is described below. Duration for these three drugs may vary; see the guidance in footnote.<sup>a</sup></b>
<b>Newborns with HIV Infection</b>	
<b>Recommended Regimen</b>	<b>Lifelong Duration Recommended<sup>b</sup></b>
<b>Three-drug</b> HIV therapy: ZDV plus 3TC plus (NVP <i>or</i> RAL)	Lifelong therapy <b>in accordance with current treatment guidelines. The ARV regimen should be individualized based on the infant's age and clinical determinants. NVP can be replaced with LPV/r when the infant reaches a postmenstrual age of <math>\geq 42</math> weeks (defined as the time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) and a postnatal age <math>\geq 14</math> days. NVP can be replaced with RAL at any age in infants who were born at a postmenstrual age of <math>\geq 37</math> weeks and who weigh <math>\geq 2</math> kg.</b>

<b>Drug</b>	<b>Drug Doses by Gestational Age at Birth</b>								
<b>ZDV</b>  <b>Note:</b> For newborns who are unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.	<b><math>\geq 35</math> Weeks Gestation at Birth</b> <i>Birth to Age 4 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 4 mg/kg per dose orally twice daily</li> </ul> <i>Age &gt;4 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 12 mg/kg per dose orally twice daily; <b>only make this dose increase for infants with confirmed HIV infection.</b></li> </ul> <b>Simplified Weight-Band Dosing for Newborns Aged <math>\geq 35</math> Weeks Gestation from Birth to 4 Weeks</b> <table border="1" style="margin-left: 20px;"> <thead> <tr> <th><b>Weight Band</b></th> <th><b>Volume of ZDV 10 mg/mL Oral Syrup Twice Daily</b></th> </tr> </thead> <tbody> <tr> <td>2 to &lt;3 kg</td> <td>1 mL</td> </tr> <tr> <td>3 to &lt;4 kg</td> <td>1.5 mL</td> </tr> <tr> <td>4 to &lt;5 kg</td> <td>2 mL</td> </tr> </tbody> </table>	<b>Weight Band</b>	<b>Volume of ZDV 10 mg/mL Oral Syrup Twice Daily</b>	2 to <3 kg	1 mL	3 to <4 kg	1.5 mL	4 to <5 kg	2 mL
	<b>Weight Band</b>	<b>Volume of ZDV 10 mg/mL Oral Syrup Twice Daily</b>							
	2 to <3 kg	1 mL							
	3 to <4 kg	1.5 mL							
4 to <5 kg	2 mL								
<b><math>\geq 30</math> to &lt;35 Weeks Gestation at Birth</b> <i>Birth to Age 2 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 2 mg/kg per dose orally twice daily</li> </ul> <i>Age 2 Weeks to 6 to 8 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 3 mg/kg per dose orally twice daily</li> </ul> <i>Age &gt;6 to 8 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 12 mg/kg per dose orally twice daily; <b>only make this dose increase for infants with confirmed HIV infection.</b></li> </ul>									
<b>&lt;30 Weeks Gestation at Birth</b> <i>Birth to Age 4 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 2 mg/kg per dose orally twice daily</li> </ul> <i>Age 4 to 8–10 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 3 mg/kg per dose orally twice daily</li> </ul> <i>Age &gt;8 to 10 Weeks:</i> <ul style="list-style-type: none"> <li>• ZDV 12 mg/kg per dose orally twice daily; <b>only make this dose increase for infants with confirmed HIV infection</b></li> </ul>									
<b>3TC</b>	<b><math>\geq 32</math> Weeks Gestation at Birth</b> <i>Birth to Age 4 Weeks:</i> <ul style="list-style-type: none"> <li>• 3TC 2 mg/kg per dose orally twice daily</li> </ul> <i>Age &gt;4 Weeks:</i> <ul style="list-style-type: none"> <li>• 3TC 4 mg/kg per dose orally twice daily</li> </ul>								

**Table 12. Antiretroviral Dosing Recommendations for Newborns (page 2 of 3)**

Drug	Drug Doses by Gestational Age at Birth																										
<b>NVP</b>	<p><b>≥37 Weeks Gestation at Birth</b></p> <p><i>Birth to Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 6 mg/kg per dose orally twice daily<sup>c</sup></li> </ul> <p><i>Age &gt;4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 200 mg/m<sup>2</sup> of BSA per dose orally twice daily; <b>only make this dose increase for infants with confirmed HIV infection.</b></li> </ul>																										
	<p><b>≥34 to &lt;37 Weeks Gestation at Birth</b></p> <p><i>Birth to Age 1 Week:</i></p> <ul style="list-style-type: none"> <li>• NVP 4 mg/kg per dose orally twice daily</li> </ul> <p><i>Age 1 to 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 6 mg/kg per dose orally twice daily</li> </ul> <p><i>Age &gt;4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• NVP 200 mg/m<sup>2</sup> of BSA per dose orally twice daily; <b>only make this dose increase for infants with confirmed HIV infection.</b></li> </ul>																										
<b>RAL</b>  <b>Note:</b> 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 ARV drugs should be started as soon as possible. <sup>7</sup>	<p><b>≥37 Weeks Gestation at Birth and Weighing ≥2 kg<sup>d</sup></b></p> <p><i>Birth to Age 6 Weeks:</i></p> <table border="1" data-bbox="370 810 1367 1312"> <thead> <tr> <th data-bbox="370 810 802 852">Body Weight</th> <th data-bbox="802 810 1367 852">Volume (Dose) of RAL 10 mg/mL Suspension</th> </tr> </thead> <tbody> <tr> <td colspan="2" data-bbox="370 852 1367 894"><b>Birth to 1 Week: Once-Daily Dosing</b></td> </tr> <tr> <td data-bbox="370 894 802 926">2 to &lt;3 kg</td> <td data-bbox="802 894 1367 926">0.4 mL (4 mg) once daily</td> </tr> <tr> <td data-bbox="370 926 802 957">3 to &lt;4 kg</td> <td data-bbox="802 926 1367 957">0.5 mL (5 mg) once daily</td> </tr> <tr> <td data-bbox="370 957 802 989">4 to &lt;5 kg</td> <td data-bbox="802 957 1367 989">0.7 mL (7 mg) once daily</td> </tr> <tr> <td colspan="2" data-bbox="370 989 1367 1031"><b>1 to 4 Weeks: Twice-Daily Dosing</b></td> </tr> <tr> <td data-bbox="370 1031 802 1062">2 to &lt;3 kg</td> <td data-bbox="802 1031 1367 1062">0.8 mL (8 mg) twice daily</td> </tr> <tr> <td data-bbox="370 1062 802 1094">3 to &lt;4 kg</td> <td data-bbox="802 1062 1367 1094">1 mL (10 mg) twice daily</td> </tr> <tr> <td data-bbox="370 1094 802 1125">4 to &lt;5 kg</td> <td data-bbox="802 1094 1367 1125">1.5 mL (15 mg) twice daily</td> </tr> <tr> <td colspan="2" data-bbox="370 1125 1367 1167"><b>4 to 6 Weeks: Twice-Daily Dosing</b></td> </tr> <tr> <td data-bbox="370 1167 802 1199">3 to &lt;4 kg</td> <td data-bbox="802 1167 1367 1199">2.5 mL (25 mg) twice daily</td> </tr> <tr> <td data-bbox="370 1199 802 1230">4 to &lt;6 kg</td> <td data-bbox="802 1199 1367 1230">3 mL (30 mg) twice daily</td> </tr> <tr> <td data-bbox="370 1230 802 1262">6 to &lt;8 kg</td> <td data-bbox="802 1230 1367 1262">4 mL (40 mg) twice daily</td> </tr> </tbody> </table>	Body Weight	Volume (Dose) of RAL 10 mg/mL Suspension	<b>Birth to 1 Week: Once-Daily Dosing</b>		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	<b>1 to 4 Weeks: Twice-Daily Dosing</b>		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	<b>4 to 6 Weeks: Twice-Daily Dosing</b>		3 to <4 kg	2.5 mL (25 mg) twice daily	4 to <6 kg	3 mL (30 mg) twice daily	6 to <8 kg	4 mL (40 mg) twice daily
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<sup>a</sup> The optimal duration of presumptive HIV therapy in newborns who are at a higher risk of perinatal HIV transmission is unknown. If possible, newborns who are at a higher risk of HIV acquisition should receive ZDV for 6 weeks. Additional medications, such as 3TC, RAL, or NVP, may need to administered for 2 to 6 weeks; the recommended durations for these drugs vary based on HIV NAT results, maternal viral load at the time of delivery, and additional risk factors for HIV transmission. Consultation with an expert in pediatric HIV is recommended when selecting a therapy duration, as this decision should be based on case-specific risk factors and interim HIV NAT results. The two-drug regimen used in NICHD-HPTN 040/PACTG 1043 for infants who were at a higher risk of HIV acquisition is described in the text (see the Two-Drug Antiretroviral Prophylaxis section).

<sup>b</sup> For ARV management after the newborn period, see the [Pediatric Antiretroviral Guidelines](#).

<sup>c</sup> This dose is an investigational NVP treatment dose recommended by the Panel; the FDA has not approved a dose of NVP for infants aged <1 month. See the Two-Drug Antiretroviral Prophylaxis section for prophylactic NVP dosing if using the NICHD-HPTN 040/PACTG 1043 prophylaxis regimen.

<sup>d</sup> 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 4–6 weeks of life. No dosing information is available for preterm infants or infants weighing <2 kg at birth.

**Key:** 3TC = lamivudine; ARV =antiretroviral; BSA = body surface area; FDA = Food and Drug Administration; IV = intravenous; LPV/r = lopinavir/ritonavir; 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; UGT = uridine diphosphate glucotransferase; ZDV = zidovudine

## Recommendations for Antiretroviral Drugs in Specific Clinical Situations

In this section 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 and achieved effective viral suppression
- Are at higher risk of transmitting HIV to their newborns, including mothers who:
  - Received neither antepartum nor intrapartum ARV drugs, *or*
  - 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
- Had acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

### ***Newborns Born to Mothers Who Achieved Viral Suppression on Antepartum/Intrapartum Antiretroviral Drugs***

The risk of HIV acquisition in newborns born to women who received ART during pregnancy and labor and who had undetectable viral loads at delivery is <1%. In the PACTG 076 study, ZDV alone reduced the incidence of perinatal HIV transmission, and ZDV is recommended as prophylaxis for neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy. The optimal minimum duration of neonatal ZDV prophylaxis has not been established in clinical trials. A 6-week ZDV regimen was studied in newborns in PACTG 076. However, evidence that supports a reduced duration of ZDV prophylaxis in infants born to women who were virologically suppressed during pregnancy and at delivery is mounting.<sup>8-10</sup> In the United Kingdom and many other European countries, a 2-week neonatal ZDV prophylaxis regimen is recommended for infants born to women who have been on ART for longer than 10 weeks **and** have had at least two documented maternal HIV viral loads <50 copies/mL at least 4 weeks apart **and** have viral loads <50 copies/mL at or after 36 weeks gestation. If all of these criteria are not fulfilled but the maternal viral load is <50 copies/mL at or after 36 weeks gestation, a 4-week course of ZDV is recommended.<sup>11</sup> Compared with the 6-week ZDV regimen, 2 to 4 weeks on a ZDV regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns.<sup>12,13</sup>

Currently, the Panel recommends a 4-week neonatal ZDV prophylaxis regimen for newborns if the mother achieved viral suppression on ART during pregnancy (defined as a confirmed HIV RNA level <50 copies/mL) at or after 36 weeks gestation, and there are no concerns related to maternal adherence. Dosing recommendations for ZDV are available for premature newborns, and an intravenous preparation of ZDV is available. Table 12 shows recommended neonatal ZDV dosing based on gestational age and birth weight.

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

**The Panel recommends that all** newborns born to mothers who had detectable viral loads at delivery, who received only intrapartum ARV drugs, or who received no ARV drugs during pregnancy or delivery are at higher risk of HIV acquisition and **should receive presumptive HIV therapy**.<sup>5,14-18</sup> Primary or acute HIV infection during pregnancy is also associated with an increased risk of perinatal transmission of HIV. Infants born to women who acquired HIV during pregnancy **should receive presumptive HIV therapy** (see [Acute HIV Infection](#)). The experience with these two strategies is described below.

## **Presumptive HIV Therapy**

Early effective treatment of HIV infection in infants restricts the viral reservoir size, reduces HIV genetic variability, and modifies the immune response.<sup>19-24</sup> As demonstrated with the “Mississippi baby” and other infants who were treated shortly after birth, early treatment may provide an opportunity for an “ART-free remission” of HIV infection.<sup>25-27</sup> Because of these potential benefits of early ART, the Panel recommends a three-drug ARV **presumptive** HIV therapy regimen consisting of ZDV, lamivudine (3TC), and either NVP (at treatment dose) or raltegravir (RAL) for newborns at higher risk of perinatal acquisition of HIV.

Although no clinical trials have compared the safety and efficacy of **presumptive** ART with single-drug or two-drug regimens, emerging data suggests that early **presumptive** HIV therapy is not associated with serious adverse events. Many infants develop anemia or neutropenia that may be drug-related regardless of whether the ARV drugs are administered as prophylaxis or treatment.<sup>28-32</sup> In a prospective cohort in Thailand, infants who received an **presumptive** HIV therapy regimen that contained ZDV, 3TC, and NVP were more likely to have Grade 2 or higher anemia at 1 and 2 months of life compared to infants who received ZDV alone (48.5% vs. 32.3%;  $P = 0.02$ ). However, there was no difference in the incidence of severe anemia between the two groups.<sup>33</sup> Additionally, in a Canadian study, nonspecific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) that were potentially attributable to medication-related adverse effects were reported among the newborns who received **presumptive** HIV therapy but not among those who received ZDV only (10.2% vs. 0%;  $P < 0.001$ ). Infants were more likely to discontinue **presumptive** HIV therapy prematurely than a regimen of ZDV alone (9.5% vs. 2.1%;  $P = 0.01$ ).<sup>29</sup>

The Centers for Disease Control and Prevention recommend a three-drug ARV regimen for HIV-post-exposure prophylaxis following occupational and non-occupational HIV exposure. HIV acquisition risk in these circumstances is often lower than for newborns at higher risk of HIV acquisition.<sup>34,35</sup> **Presumptive** HIV therapy pharmacokinetic (PK) and safety data has provided reassuring evidence for its use in the neonatal period. Although the use of NVP to prevent perinatal HIV transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels which are  $\geq 10$ -fold lower than targeted therapeutic levels. However, recent studies of therapeutic doses of NVP and RAL have established safe doses that achieve targeted PK parameters.<sup>36-40</sup>

At this time, if a **presumptive** HIV therapy regimen is required, the Panel recommends using a combination of ZDV, 3TC, and NVP (treatment dose) or ZDV, 3TC, and RAL (see **Tables 11 and 12**). The optimal duration of **presumptive** HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Some Panel members opt to discontinue additional medications if birth nucleic acid test (NAT) results are negative, while others would continue **presumptive** HIV therapy for 2 to 6 weeks depending on the risk of HIV transmission. In all cases, ZDV should be continued for 6 weeks. If HIV infection is confirmed and the infant is receiving NVP, a switch from NVP to lopinavir/ritonavir (LPV/r) is recommended when the infant reaches a postmenstrual age **(defined as the time from the first day of the mother’s last menstrual period to birth plus the time elapsed after birth)** of  $\geq 42$  weeks and a postnatal age of  $\geq 14$  days; a switch to RAL can be made at any age (see **What to Start** in the **Pediatric Antiretroviral Guidelines**). Consulting an expert in pediatric HIV is recommended when selecting a therapy duration based on case-specific risk factors and interim HIV NAT results.

## **Two-Drug Antiretroviral Prophylaxis**

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 receive one of three newborn prophylaxis regimens: the standard 6-week ZDV regimen; 6 weeks of ZDV plus three doses of NVP given during the first week of life (first dose given at birth or within 48 hours of birth, second dose 48 hours after the first dose, and third dose 96 hours after the second dose); and 6 weeks of ZDV plus 2 weeks of 3TC plus nelfinavir (NFV).

Forty-one percent of the mothers received ZDV during labor. The risk of intrapartum transmission was significantly lower in the two-drug and three-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of ZDV alone;  $P = 0.046$  for each experimental arm vs. ZDV alone).<sup>5</sup> The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in three of 53 participants (5.7%) with *in utero* infection who were treated with ZDV alone, and in six of 33 participants (18.2%) who were treated with ZDV plus NVP ( $P > 0.05$ ). In addition, the third drug in the three-arm regimen was NFV, which has highly variable PKs in this age group and did not reach the NFV target plasma concentration in 46% of study participants.<sup>41</sup>

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

### Choosing between Presumptive HIV Therapy and Two-Drug Antiretroviral Prophylaxis

Because there is a spectrum of transmission risk that depends on maternal viral load and other maternal and infant factors **and** there are no randomized trials that have compared the safety and efficacy of presumptive HIV therapy and two-drug ARV prophylaxis, experts have differing opinions about when to initiate presumptive HIV therapy and when to initiate two-drug prophylaxis. For instance, among women who received ARV drugs during pregnancy but who have a detectable viral load near delivery (on or after 36 weeks gestation), the level of maternal viremia that would prompt the use of a two-drug ARV prophylaxis regimen or presumptive HIV therapy is not definitively known.

In two large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had a viral load  $< 50$  copies/mL at delivery. Rates of transmission in these studies increased to 1.1% and 1.5% when viral load was 50 to 399 copies/mL, and 2.8% and 4.1% when viral load was  $> 400$  copies/mL.<sup>42,43</sup> While most Panel members would recommend initiating presumptive HIV therapy with any detectable level of viremia near delivery, others may opt for a two-drug prophylaxis regimen if maternal viral load was less than 200 to 400 copies/mL. Emerging data about the lack of serious safety issues associated with presumptive HIV therapy in newborns is reassuring, even though nonserious adverse events may occur more frequently.

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

Consulting an expert in pediatric HIV or the [National Perinatal HIV Hotline](https://www.hiv.gov/national-perinatal-hiv-hotline) (1-888-448-8765) is recommended when selecting a regimen based on case-specific risk factors.

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

Expedited HIV testing is recommended during labor for women with unknown HIV status; if testing is not performed during labor, it should be performed as soon as possible after birth for the mothers and/or their newborns (see [Maternal HIV Testing and Identification of Perinatal HIV Exposure](#)). Expedited test results should be available within 60 minutes. If maternal or infant expedited testing is positive, the newborn **should immediately initiate presumptive 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 not all states allow HIV testing in infants without parental consent.

A nursing mother who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result should 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.<sup>44</sup>

### ***Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus***

The optimal ARV regimen for newborns born to women with ARV drug-resistant virus is unknown. Although some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility,<sup>45</sup> perinatal transmission of multidrug-resistant virus does occur.<sup>46-51</sup> It is also unknown whether resistant virus in the mother increases the antepartum/intrapartum risk of HIV acquisition by the infant. A recently reported secondary analysis of data from the NICHD-HPTN 040/PACTG 1043 study demonstrated that the risk of perinatal transmission was not related to the presence of drug resistance mutations in mothers who had not received ARV drugs prior to the start of the study (adjusted odds ratio 0.8; 95% confidence interval, 0.4–1.5).<sup>51</sup> 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](https://www.hivhotline.org/) (1-888-448-8765). 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.

### ***Newborns with HIV Infection***

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and were intended to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT results meant that neonatal infections were generally not diagnosed during the first weeks of life. HIV NAT results are now available within a few days, and HIV in newborns is being diagnosed as early as the first days of life in many centers. A positive HIV NAT must be repeated to confirm HIV. However, 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 early treatment (before age 2 weeks) will conclusively lead to prolonged remission or better outcomes in newborns with HIV is lacking.

Information regarding the safety of early treatment of HIV in newborns has been reported from two studies. In the IMPAACT P1115 study, 54 infants with HIV initiated **presumptive** HIV therapy between 0.4 and 40 hours of life. Grade 3 or 4 related events, most of which were hematologic, occurred in 22 of 54 infants (41%) through 52 weeks of the study.<sup>30</sup> Forty infants with HIV in Botswana initiated NVP plus ZDV plus 3TC at a median age of 2 days (range 1–5 days) and transitioned to LPV/r plus ZDV plus 3TC at approximately 2 weeks of age. These infants had minimal toxicity during the first 12 weeks of treatment. Only one instance of Grade 3 neutropenia was reported and no instances of Grade 3 or 4 anemia were reported.<sup>32</sup>

Earlier diagnosis of HIV in newborns and the increasing use of **presumptive** 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 data are still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same, with the important exception of **NVP** (see the [Pediatric Antiretroviral Guidelines](#)).

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

- From birth in term and preterm newborns: [ZDV](#), [3TC](#), [NVP](#)
- From birth in term newborns: [emtricitabine](#), [RAL](#)
- From age 2 weeks in term newborns: [LPV/r](#)

Dosing recommendations for *premature* newborns are available for ZDV, 3TC, and NVP only. Neonatal dosing advice, including dosing advice for premature newborns, is summarized in Table 12. For more detailed information about neonatal dosing recommendations and considerations when using these drugs, please see the [Pediatric Antiretroviral Guidelines](#).

### ***Newborns of Mothers Who Receive an HIV Diagnosis 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 [Counseling and Managing Women Living with HIV in the United States Who Desire to Breastfeed](#)).<sup>52</sup>

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.<sup>53</sup> Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than those whose mothers have chronic HIV infection,<sup>54</sup> because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 count.<sup>55</sup>

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 over a prolonged period rather than during a single exposure to the virus.<sup>56</sup>

Several studies of newborns who were breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn NVP, 3TC, LPV/r, or NVP plus ZDV can reduce the risk of postnatal infection during breastfeeding.<sup>57-61</sup> No trials have evaluated the use of multidrug-regimens to prevent transmission after cessation of breastfeeding in mothers with acute HIV infection.

Given the higher risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some Panel members is to offer **presumptive** HIV therapy until the infant's HIV status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of **presumptive** HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational HIV exposure.<sup>56</sup> When making decisions about ARV management, clinicians should consult a pediatric HIV specialist and counsel the parents on the potential risks and benefits of a particular treatment strategy. The [National Perinatal HIV Hotline](#) (1-888-448-8765) can provide referrals to local or regional pediatric HIV specialists.

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

Resistance testing should be performed, and the ART regimen should be modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

## Short-Term Antiretroviral Drug Safety

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

Other than ZDV, 3TC is the NRTI with the most clinical experience for neonatal prophylaxis. In early studies, neonatal exposure to combination ZDV/3TC was generally limited to 1<sup>17,62,63</sup> or 2 weeks.<sup>5</sup> Six weeks of ZDV/3TC exposure in newborns has also been reported. These studies suggest that hematologic toxicity may be greater with ZDV/3TC than with ZDV alone, although the newborns in these studies also had *in utero* exposure to maternal HIV therapy that may have contributed to the toxicity.

In a French study, more cases of severe anemia and neutropenia were observed in newborns who were exposed to 6 weeks of ZDV/3TC for prophylaxis plus maternal antepartum ZDV/3TC than in a historical cohort of newborns who were exposed only to maternal and newborn ZDV. Anemia was reported in 15% of newborns and neutropenia was reported in 18% of newborns who were exposed to ZDV/3TC, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.<sup>64</sup> Similarly, in a Brazilian study of maternal antepartum ZDV/3TC and 6-week newborn ZDV/3TC prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia seen in 13% of newborns.<sup>65</sup>

Experience with other NRTI drugs for neonatal prophylaxis is more limited.<sup>66,67</sup> Hematologic and mitochondrial toxicity may be more common with exposure to multiple NRTI drugs than with exposure to a single NRTI.<sup>64,68-71</sup>

In rare cases, chronic multiple-dose NVP prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.<sup>72</sup> These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose NVP or the two-drug ZDV regimen plus three doses of NVP in the first week of life used in NICHD-HPTN 040/PACTG 1043, or in breastfeeding newborns receiving NVP prophylaxis daily for 6 weeks to 18 months to prevent transmission of HIV via breast milk.<sup>5,57-59,61,73</sup>

The Food and Drug Administration (FDA) recently approved infant dosing of RAL for term neonates aged  $\geq 37$  weeks gestation at birth and weighing  $\geq 2$  kg. Dosing information for RAL is not available for preterm or low birthweight infants. Infant RAL dosing needs to be increased at 1 week and 4 weeks of age. RAL is metabolized by uridine diphosphate glucuronosyltransferase (UGT) 1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. In addition, bilirubin and RAL may compete for albumin binding sites, and extremely elevated neonatal plasma RAL concentrations could pose a risk of kernicterus.<sup>74</sup> IMPAACT P1110 is a Phase 1, multicenter trial that enrolled full-term neonates who were exposed to HIV and who were at risk of acquiring perinatal HIV-1 infection, with or without *in utero* RAL exposure. Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for  $\leq 6$  weeks from birth and followed for 24 weeks. There were no drug-related clinical adverse reactions, and only three laboratory adverse reactions were observed: one case of Grade 4 transient neutropenia in an infant receiving a ZDV-containing regimen; and two cases of bilirubin elevations (one Grade 1 and one Grade 2) that were considered nonserious and did not require specific therapy<sup>75</sup> (see the [Raltegravir](#) section of the [Pediatric Antiretroviral Guidelines](#) for additional information).

The safety and PK data on daily dosing from P1110 are from RAL-naïve infants whose mothers did not receive RAL; data collection from infants born to mothers who were receiving RAL is ongoing. However, the FDA currently recommends delaying the first dose of RAL in infants for 24 to 48 hours after birth if the mother received RAL 2 to 24 hours before delivery, and the Panel believes that this recommendation is reasonable based on current data about clearance of the drug in RAL-exposed infants.

Of the protease inhibitors, pediatric drug formulations are available for LPV/r, ritonavir (RTV), darunavir,

tipranavir, and fosamprenavir; however, the use of these drugs in neonates during 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. The enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (two sets of twins) who initiated LPV/r at birth developed heart block that resolved after drug discontinuation.<sup>76,77</sup> In studies of adults, both RTV and LPV/r caused 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 administering LPV/r during the neonatal period, an association not found with ZDV. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to LPV/r *in utero* than in those exposed only during 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.<sup>78</sup>

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,<sup>79</sup> predominantly in preterm neonates, the FDA now recommends that LPV/r oral solution **not be administered** to neonates before the infant reaches a postmenstrual age (defined as time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth) of  $\geq 42$  weeks and a postnatal age of  $\geq 14$  days.<sup>80</sup> However, the ANRS 12174 study randomized 1,273 newborns to receive either LPV/r (n = 615) or 3TC (n = 621) 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 weighing  $> 2$  kg were randomized. The frequency of clinical and biological severe adverse events did not differ between the groups, suggesting that LPV/r is safe to use in term newborns aged 7 days and older.<sup>81</sup> At this time, the Panel **does not recommend** the use of LPV/r before a postmenstrual age of 42 weeks **(defined as time from the first day of the mother's last menstrual period to birth plus the time elapsed after birth)** and a postnatal age of  $\geq 14$  days.

## References

1. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *N Engl J Med*. 1998;339(20):1409-1414. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9811915>.
2. Van Rompay KK, Otsyula MG, Marthas ML, Miller CJ, McChesney MB, Pedersen NC. Immediate zidovudine treatment protects simian immunodeficiency virus-infected newborn macaques against rapid onset of AIDS. *Antimicrob Agents Chemother*. 1995;39(1):125-131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7695293>.
3. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl) adenine. *Science*. 1995;270(5239):1197-1199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7502044>.
4. Bottiger D, Johansson NG, Samuelsson B, et al. Prevention of simian immunodeficiency virus, SIVsm, or HIV-2 infection in cynomolgus monkeys by pre- and postexposure administration of BEA-005. *AIDS*. 1997;11(2):157-162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9030361>.
5. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716975>.
6. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS*. 1995;9(9):F7-11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8527070>.
7. Lommerse J, Clarke D, Kerbusch T, et al. Maternal-neonatal raltegravir population pharmacokinetics modeling: implications for initial neonatal dosing. *CPT Pharmacometrics Syst Pharmacol*. 2019. Available at: <https://www.ncbi>.

[nlm.nih.gov/pubmed/31215170](http://nlm.nih.gov/pubmed/31215170).

8. de Ruiter A, Mercey D, Anderson J, et al. British HIV association and children's HIV association guidelines for the management of HIV infection in pregnant women 2008. *HIV Med.* 2008;9(7):452-502. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18840151>.
9. Ferguson W, Goode M, Walsh A, Gavin P, Butler K. Evaluation of 4 weeks' neonatal antiretroviral prophylaxis as a component of a prevention of mother-to-child transmission program in a resource-rich setting. *Pediatr Infect Dis J.* 2011;30(5):408-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21266939>.
10. Neubert J, Pfeffer M, Borkhardt A, et al. Risk adapted transmission prophylaxis to prevent vertical HIV-1 transmission: effectiveness and safety of an abbreviated regimen of postnatal oral zidovudine. *BMC Pregnancy Childbirth.* 2013;13:22. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23347580>.
11. British HIV Association. BHIVA guidelines on the management of HIV in pregnancy and postpartum 2018 (2019 interim update). 2019. Available at: <https://www.bhiva.org/pregnancy-guidelines>.
12. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J.* 2010;29(4):376-379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19949355>.
13. Nguyen TTT, Kobbe R, Schulze-Sturm U, et al. Reducing hematologic toxicity with short course postexposure prophylaxis with zidovudine for HIV-1 exposed infants with low transmission risk. *Pediatr Infect Dis J.* 2019;38(7):727-730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31033907>.
14. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. *N Engl J Med.* 1999;341(6):385-393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10432323>.
15. Garcia PM, Kalish LA, Pitt J, et al. Maternal levels of plasma human immunodeficiency virus type 1 RNA and the risk of perinatal transmission. Women and infants transmission study group. *N Engl J Med.* 1999;341(6):394-402. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10432324>.
16. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr.* 2002;29(5):484-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11981365>.
17. Petra Study Team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2002;359(9313):1178-1186. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11955535>.
18. Lallemand M, Jourdain G, Le Coeur S, et al. A trial of shortened zidovudine regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV Prevention Trial (Thailand) Investigators. *N Engl J Med.* 2000;343(14):982-991. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11018164>.
19. Persaud D, Ray SC, Kajdas J, et al. Slow human immunodeficiency virus type 1 evolution in viral reservoirs in infants treated with effective antiretroviral therapy. *AIDS Res Hum Retroviruses.* 2007;23(3):381-390. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17411371>.
20. Luzuriaga K, Tabak B, Garber M, et al. HIV type 1 (HIV-1) proviral reservoirs decay continuously under sustained virologic control in HIV-1-infected children who received early treatment. *J Infect Dis.* 2014;210(10):1529-1538. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24850788>.
21. Persaud D, Patel K, Karalius B, et al. Influence of age at virologic control on peripheral blood human immunodeficiency virus reservoir size and serostatus in perinatally infected adolescents. *JAMA Pediatrics.* 2014;168(12):1138-1146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25286283>.
22. Rainwater-Lovett K, Ziemniak C, Watson D, et al. Paucity of intact non-induced provirus with early, long-term antiretroviral therapy of perinatal HIV infection. *PLoS One.* 2017;12(2):e0170548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28178277>.

23. Rocca S, Zangari P, Cotugno N, et al. Human immunodeficiency virus (HIV)-antibody repertoire estimates reservoir size and time of antiretroviral therapy initiation in virally suppressed perinatally HIV-infected children. *J Pediatric Infect Dis Soc*. 2018. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30169837>.
24. Shiau S, Abrams EJ, Arpadi SM, Kuhn L. Early antiretroviral therapy in HIV-infected infants: can it lead to HIV remission? *Lancet HIV*. 2018;5(5):e250-e258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29739699>.
25. Persaud D, Gaye H, et al. Absence of detectable HIV-1 viremia following treatment cessation in an infant. *N Engl J Med*. 2013;369(19):1828-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24152233>
26. Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25251719>.
27. Violari A, Cotton MF, Kuhn L, et al. A child with perinatal HIV infection and long-term sustained virological control following antiretroviral treatment cessation. *Nat Commun*. 2019;10(1):412. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30679439>.
28. Bitnun A, Samson L, Chun TW, et al. Early initiation of combination antiretroviral therapy in HIV-1-infected newborns can achieve sustained virologic suppression with low frequency of CD4+ T cells carrying HIV in peripheral blood. *Clin Infect Dis*. 2014;59(7):1012-1019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24917662>.
29. Kakkar FW, Samson L, Vaudry W, et al. Safety of combination antiretroviral prophylaxis in high-risk HIV-exposed newborns: a retrospective review of the Canadian experience. *J Int AIDS Soc*. 2016;19(1):20520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26880241>.
30. Persaud D, Chadwick E, Tierney C, et al. Virologic response to very early ART in neonates with *in utero* HIV: IMPAACT P115. Abstract 799. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/virologic-response-very-early-art-neonates-utero-hiv-impact-p1115>.
31. Ruel T, Hazra R, Jean-Philippe P, et al. Outcomes of neonates with rapid hiv treatment in us: treating infants early study. Abstract 802. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <https://www.croiconference.org/sessions/outcomes-neonates-rapid-hiv-treatment-us-treating-infants-early-study>.
32. Shapiro R, Bennett K, Hughes M, et al. Safety and efficacy of starting antiretroviral therapy in the first week of life. Abstract 826. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <https://www.croiconference.org/sessions/safety-and-efficacy-starting-antiretroviral-therapy-first-week-life>.
33. Anugulruengkitt S, Suntarattiwong P, Ounchanum P, et al. Safety of 6-week neonatal triple-combination antiretroviral postexposure prophylaxis in high-risk HIV-exposed infants. *Pediatr Infect Dis J*. 2019;38(10):1045-1050. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31365477>.
34. Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV—United States. 2016. Available at: <http://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf> .
35. Kuhar DT, Henderson DK, Struble KA, et al. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. *Infect Control Hosp Epidemiol*. 2013;34(9):875-892. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23917901>.
36. Lau E, Brophy J, Samson L, et al. Nevirapine pharmacokinetics and safety in neonates receiving combination antiretroviral therapy for prevention of vertical HIV transmission. *J Acquir Immune Defic Syndr*. 2017;74(5):493-498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28114187>.
37. Cressey TR, Punyawudho B, Le Coeur S, et al. Assessment of nevirapine prophylactic and therapeutic dosing regimens for neonates. *J Acquir Immune Defic Syndr*. 2017;75(5):554-560. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28489732>.
38. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir*

*Immune Defic Syndr.* 2014;67(3):310-315. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25162819>.

39. Clarke DF, Wong RJ, Wenning L, Stevenson DK, Mirochnick M. Raltegravir in vitro effect on bilirubin binding. *Pediatr Infect Dis J.* 2013;32(9):978-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23470680>.
40. Clarke DF, Penazzato M, Capparelli E, et al. Prevention and treatment of HIV infection in neonates: evidence base for existing WHO dosing recommendations and implementation considerations. *Expert Rev Clin Pharmacol.* 2018;11(1):83-93. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29039686>.
41. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nelfinavir and lamivudine pharmacokinetics during the first two weeks of life. *Pediatr Infect Dis J.* 2011;30(9):769-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21666540>.
42. Mandelbrot L, Tubiana R, Le Chenadec J, et al. No perinatal HIV-1 transmission from women with effective antiretroviral therapy starting before conception. *Clin Infect Dis.* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26197844>.
43. Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000-2011. *AIDS.* 2014;28(7):1049-1057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24566097>.
44. American Academy of Pediatrics (AAP). Breastfeeding and the use of human milk. 2012. Available at: <http://www.pediatrics.org/cgi/doi/10.1542/peds.2011-3552>.
45. Bauer GR, Colgrove RC, Larussa PS, Pitt J, Welles SL. Antiretroviral resistance in viral isolates from HIV-1-transmitting mothers and their infants. *AIDS.* 2006;20(13):1707-1712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16931934>.
46. De Jose MI, Ramos JT, Alvarez S, Jimenez JL, Munoz-Fernandez MA. Vertical transmission of HIV-1 variants resistant to reverse transcriptase and protease inhibitors. *Arch Intern Med.* 2001;161(22):2738-2739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11732941>.
47. Desai N, Mathur M. Selective transmission of multidrug resistant HIV to a newborn related to poor maternal adherence. *Sex Transm Infect.* 2003;79(5):419-421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14573842>.
48. Cohan D, Feakins C, Wara D, et al. Perinatal transmission of multidrug-resistant HIV-1 despite viral suppression on an enfuvirtide-based treatment regimen. *AIDS.* 2005;19(9):989-990. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15905684>.
49. Fogel J, Li Q, Taha TE, et al. Initiation of antiretroviral treatment in women after delivery can induce multiclass drug resistance in breastfeeding HIV-infected infants. *Clin Infect Dis.* 2011;52(8):1069-1076. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21460326>.
50. Zeh C, Weidle PJ, Nafisa L, et al. HIV-1 drug resistance emergence among breastfeeding infants born to HIV-infected mothers during a single-arm trial of triple-antiretroviral prophylaxis for prevention of mother-to-child transmission: a secondary analysis. *PLoS Med.* 2011;8(3):e1000430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21468304>.
51. Yeganeh N, Kerin T, Ank B, et al. Human immunodeficiency virus antiretroviral resistance and transmission in mother-infant pairs enrolled in a large perinatal study. *Clin Infect Dis.* 2018;66(11):1770-1777. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29272365>.
52. Committee On Pediatric AIDS. Infant feeding and transmission of human immunodeficiency virus in the United States. *Pediatrics.* 2013;131(2):391-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23359577>.
53. Kuhn L, Reitz C, Abrams EJ. Breastfeeding and AIDS in the developing world. *Curr Opin Pediatr.* 2009;21(1):83-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19242244>.
54. Van de Perre P, Lepage P, Homsy J, Dabis F. Mother-to-infant transmission of human immunodeficiency virus by breast milk: presumed innocent or presumed guilty? *Clin Infect Dis.* 1992;15(3):502-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1445596>.
55. Daar ES. Virology and immunology of acute HIV type 1 infection. *AIDS Res Hum Retroviruses.* 1998;14 Suppl 3:S229-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9814948>.

56. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. department of health and human services. *MMWR Recomm Rep*. 2005;54(RR-2):1-20. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15660015>.
57. Six Week Extended-Dose Nevirapine Study Team, Bedri A, Gudetta B, et al. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet*. 2008;372(9635):300-313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18657709>.
58. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. *N Engl J Med*. 2008;359(2):119-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18525035>.
59. Chasela CS, Hudgens MG, Jamieson DJ, et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmission. *N Engl J Med*. 2010;362(24):2271-2281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20554982>.
60. Kilewo C, Karlsson K, Massawe A, et al. Prevention of mother-to-child transmission of HIV-1 through breast-feeding by treating infants prophylactically with lamivudine in Dar es Salaam, Tanzania: the Mitra Study. *J Acquir Immune Defic Syndr*. 2008;48(3):315-323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18344879>.
61. Taha T, Flynn P, Cababasay M, et al. Comparing maternal triple antiretrovirals (mART) and infant nevirapine (iNVP) prophylaxis for the prevention of mother to child transmission (MTCT) of HIV during breastfeeding (Bf). 21st International AIDS Conference. 2016. Durban, SA.
62. Moodley J, Moodley D, Pillay K, et al. Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis*. 1998;178(5):1327-1333. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9780252>.
63. Moodley D, Moodley J, Coovadia H, et al. A multicenter randomized controlled trial of nevirapine versus a combination of zidovudine and lamivudine to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J Infect Dis*. 2003;187(5):725-735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12599045>.
64. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA*. 2001;285(16):2083-2093. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11311097>.
65. Lambert JS, Nogueira SA, Abreu T, et al. A pilot study to evaluate the safety and feasibility of the administration of AZT/3TC fixed dose combination to HIV infected pregnant women and their infants in Rio de Janeiro, Brazil. *Sex Transm Infect*. 2003;79(6):448-452. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14663118>.
66. Gray G, Violari A, McIntyre J, et al. Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: its role in preventing HIV infection in infants. *J Acquir Immune Defic Syndr*. 2006;42(2):169-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16639342>.
67. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalating study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr*. 2002;29(5):455-463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11981361>.
68. Torres SM, Walker DM, Carter MM, et al. Mutagenicity of zidovudine, lamivudine, and abacavir following in vitro exposure of human lymphoblastoid cells or *in utero* exposure of CD-1 mice to single agents or drug combinations. *Environ Mol Mutagen*. 2007;48(3-4):224-238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17358033>.
69. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S, Enquete Perinatale Francaise Study Group. Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants. *AIDS*. 2003;17(14):2053-2061. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14502008>.
70. Pacheco SE, McIntosh K, Lu M, et al. Effect of perinatal antiretroviral drug exposure on hematologic values in HIV-uninfected children: An analysis of the women and infants transmission study. *J Infect Dis*. 2006;194(8):1089-1097. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16991083>.

71. Feiterna-Sperling C, Weizsaecker K, Buhner C, et al. Hematologic effects of maternal antiretroviral therapy and transmission prophylaxis in HIV-1-exposed uninfected newborn infants. *J Acquir Immune Defic Syndr*. 2007;45(1):43-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17356471>.
72. Hitti J, Frenkel LM, Stek AM, et al. Maternal toxicity with continuous nevirapine in pregnancy: results from PACTG 1022. *J Acquir Immune Defic Syndr*. 2004;36(3):772-776. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15213559>.
73. Coovadia HM, Brown ER, Fowler MG, et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;379(9812):221-228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22196945>.
74. Clarke DF, Wong RJ, Wenning L, Stephenson DK, Mirochnick M. Raltegravir In vitro effect on bilirubin binding. *Pediatr Infect Dis J*. 2013;32(9):978-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23470680>.
75. Raltegravir [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022145s038,205786s007,0203045s0151bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022145s038,205786s007,0203045s0151bl.pdf)
76. Lopriore E, Rozendaal L, Gelinck LB, Bokenkamp R, Boelen CC, Walther FJ. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS*. 2007;21(18):2564-2565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025905>.
77. McArthur MA, Kalu SU, Foulks AR, Aly AM, Jain SK, Patel JA. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J*. 2009;28(12):1127-1129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19820426>.
78. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. 2011;306(1):70-78. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21730243>.
79. Boxwell D, Cao K, Lewis L, Marcus K, Nikhar B. Neonatal toxicity of Kaletra oral solution: LPV, ethanol or propylene glycol? Presented at: 18th Conference on Retroviruses and Opportunistic Infections. 2011. Boston, MA.
80. Food and Drug Administration. FDA drug safety communication: serious health problems seen in premature babies given kaletra (lopinavir/ritonavir) oral solution. 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm246002.htm>.
81. Nagot N, Kankasa C, Tumwine JK, et al. Extended pre-exposure prophylaxis with lopinavir-ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial. *Lancet*. 2016;387(10018):566-573. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26603917>.

## Specific Considerations in Antiretroviral Therapy Use in Adolescents with HIV (Last updated April 14, 2020; last reviewed April 14, 2020)

### Panel's Recommendations

- All adolescents living with HIV should receive maximally suppressive antiretroviral (ARV) therapy; 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**). See [What to Start](#) and [Management of Children Receiving Antiretroviral Therapy](#) for more information.
- All adolescents with HIV should be screened for mental health disorders and substance use disorders (**AII**).
- Reproductive health issues—including pregnancy intentions, contraceptive methods, safer sex techniques to prevent transmission of HIV and other sexually transmitted infections, pre-exposure prophylaxis for partners, pregnancy planning, and preconception care—should be discussed regularly (**AI**).
- Providers should be aware of potential interactions between specific ARV medications and hormonal contraceptives that could lower contraceptive efficacy (**AII\***).
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings (**AIII**).

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

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

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

## Background

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

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

## 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 to consider when determining the dosing for antiretroviral (ARV) drugs that have a narrow therapeutic index (e.g., the protease inhibitor [PI] atazanavir) and that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.<sup>9</sup>

In addition, many 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.

## Timing and Selection of Antiretroviral Therapy

All adolescents living with HIV (like all people living with HIV), should initiate ART as soon as possible. Recommendations for ART dosing in adolescents with sexual maturity ratings (SMRs) 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 with SMRs between 4 and 5 are available in the What to Start section of the Adult and Adolescent Antiretroviral Guidelines. **Optimizing and simplifying treatment may be especially important when treating adolescents, as this can help improve adherence (see [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#)).**

Clinicians who are treating adolescents of childbearing potential should consider additional factors before initiating ART, including potential drug interactions with contraception and the safety of using certain ARV drugs before conception or during pregnancy (see the Contraception, Pregnancy, and Antiretroviral Therapy section below).

## 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 with HIV, as they are frequently inexperienced with managing their own health care and may lack health insurance. **Adolescents with perinatally acquired HIV infection are at risk for neurocognitive impairment, which can also interfere with medication adherence.**<sup>10</sup> Many are also at risk for mental health co-morbidities, including psychiatric, behavioral, and substance use disorders that may interfere with adherence to ART.<sup>11,12</sup> Compared with adults, youth have lower rates of viral suppression and higher rates of virologic rebound and loss to follow up.<sup>13-15</sup> 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.<sup>3</sup>

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternatives to changing the ARV regimen can include, but are not limited to: simplifying treatment to a once-daily regimen or an FDC tablet, using cell phone alerts and other eHealth approaches to remind patients to take their medication and attend clinic visits, initiating a short-term deferral of treatment until adherence improves or while adherence-related problems 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 regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient's clinical and laboratory status should be monitored carefully. **The use of long-acting oral and injectable ARV regimens for adolescents are currently being investigated, and these regimens may provide an alternative approach for adolescents with adherence challenges.**

## Mental Health and Substance Use Concerns in Adolescents

Many factors can increase the risk of adverse mental health outcomes among adolescents with perinatally acquired HIV, including long-term medical treatment for a chronic disease, hospitalizations, stigma, the neurocognitive impacts of HIV, parental psychiatric and substance use disorders, and family and caregiver stress and loss. The prevalence of mental health disorders in youth with perinatally acquired HIV is high, with nearly 70% of these adolescents meeting the criteria for a psychiatric disorder at some point in their lives.<sup>11,16-18</sup> 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 (see [Substance Use Disorders and HIV](#) in the Adult and Adolescent Antiretroviral Guidelines).<sup>12,19-21</sup>

Interventions that address mental health in youth with perinatally acquired HIV include pharmacologic interventions; behavioral modification; and individual, family, and group counselling. However, there is a lack of data on the effectiveness of these interventions on HIV clinical outcomes.<sup>22-24</sup> **Current evidence suggests that a combination of tailored psychotherapy (such as cognitive behavioral therapy) and pharmacotherapy can reduce depressive symptoms in adolescents with HIV; however, clinicians who prescribe pharmacotherapy for depression must take potential interactions with ARV drugs into account.**<sup>25,26</sup> 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 \(CRAFT\)](#), may be used. Providers should also consider emerging substance use trends when screening adolescents.<sup>27</sup> **Further guidance on screening tools for substance use and mental health is provided by the [National Institute on Drug Abuse's Screening and Assessment Tools Chart](#).**

## Sexually Transmitted Infections in Adolescents

Clinicians should discuss the risk of sexually transmitted infections (STIs) with their patients. All adolescents with HIV should be screened for STIs and treated appropriately. Clinicians should regularly obtain a detailed sexual history for adolescents 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.<sup>28</sup> For a more detailed discussion of STIs, see the most recent Centers for Disease Control and Prevention guidelines,<sup>29</sup> [Human Papillomavirus Disease](#) in the Adult and Adolescent Opportunistic Infection Guidelines, and [Human Papillomavirus](#) in the Pediatric Opportunistic Infection Guidelines. All female adolescents with HIV who are sexually active should receive gynecologic services. All adolescents should receive three doses of the 9-valent human papillomavirus vaccination.

## Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents with HIV may initiate sexual activity before or after puberty. Sexually active adolescents are at risk for unintended pregnancy. Approximately half of pregnancies in the United States, including those among women with HIV, are unintended or unplanned.<sup>30,31</sup> Providers should regularly assess adolescents' desires to become pregnant or avoid pregnancy (also known as their pregnancy intentions). Family planning counseling, including a discussion of the risks of sexual HIV transmission, perinatal HIV transmission, and methods for reducing these risks, should be provided to all youth. Reproductive health options, such as pregnancy planning, preconception care, contraceptive methods, pre-exposure prophylaxis for partners, and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of sexual HIV transmission, should be discussed regularly (see [U.S. Medical Eligibility Criteria for Contraceptive Use](#)).<sup>32</sup> For additional information, refer 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 When One or Both Partners are Living with HIV](#). The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.<sup>33</sup>

The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for a female adolescent. The most vulnerable period in fetal organogenesis is the first trimester, often before pregnancy is recognized. When treating adolescents of childbearing potential, clinicians should carefully

review the potential toxicities of ARV drugs and consider making any necessary changes to a regimen as promptly as possible (e.g., before conception, when possible). For additional information, please see the [Teratogenicity](#) section of the Perinatal Guidelines. Readers should consult [Table 5](#) in the [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#) section of 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. **Exposure to dolutegravir (DTG) around the time of conception has been associated with a small, but significant, increase in the risk of infant neural tube defects that** should be considered when discussing ART options with female adolescents and their caregivers. Specific recommendations about the initiation and use of DTG in adolescents and women of childbearing potential and in those who are pregnant **or trying to conceive** 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, Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D: Dolutegravir Counseling Guide for Health Care Providers](#)).

### ***Interactions Between Contraceptives and Antiretroviral Drugs***

Women with HIV can use all available contraceptive methods, including hormonal contraceptives, implantable devices, intrauterine devices, the transdermal patch, and vaginal ring.<sup>34</sup>

Several PIs and non-nucleoside reverse transcriptase inhibitors alter the metabolism of oral contraceptives, which may theoretically reduce the efficacy of oral contraceptive agents or increase the risk of estrogen-related or progestin-related adverse effects (see [Drug-Drug Interactions](#) in the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#)).<sup>35-37</sup> Integrase strand transfer inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives.<sup>38</sup> 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 coadministration of 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](#)). 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](#) for more details about choosing an ARV regimen for pregnant women with HIV, including adolescents, and guidance regarding the use of DTG during pregnancy. Pregnancies can be expected as girls with perinatally acquired HIV enter adolescence and young adulthood.<sup>39,40</sup> 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 who acquired HIV by horizontal transmission, and unplanned pregnancy appears to be a frequent occurrence.<sup>40-42</sup> 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.<sup>43-47</sup>

### ***Special Considerations for Adolescents with HIV Who Are Sexual Minorities***

**Adolescence represents a period of emerging recognition of sexual identity. Adolescents who are lesbian, gay, bisexual, transgender, or nonbinary and who are living with HIV require both culturally competent providers and tailored medical care. Health care providers should ask patients nonjudgmental questions about their sexual and gender identity to determine whether they require specific medical and support services. It is important to consider the possibility of drug-drug interactions in adolescents who are receiving both ART and**

gender-affirming hormone therapy. Additional resources for the care of these adolescents can be found in the [Adolescents and Young Adults with HIV](#) section and the [Transgender People with HIV](#) section of the [Adult and Adolescent Antiretroviral Guidelines](#).

## Transitioning Adolescents into Adult HIV Care Settings

Facilitating a seamless transition for adolescents with HIV from their pediatric/adolescent care clinic to adult care is important but challenging.<sup>48-50</sup> Many adolescents disengage from care during the transition to adult care, putting them at risk for HIV progression and transmission to partners.<sup>51-53</sup> Pediatric and adolescent care 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 their parents and/or caregivers. A 2005 study described transition as “a multifaceted, active process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child- to the adult-focused health care system.”<sup>54</sup> 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 care providers. These providers often expect patients to assume a greater level of responsibility for their care, and adolescents may be uncomfortable with providers with whom they do not have a long-standing relationship.

One multisite study in the United States found that adolescents who transitioned to adult care at an older age reported greater satisfaction with their care than those who transitioned at a younger age. Additionally, adolescents who reported being able to perform certain tasks that were related to their care (e.g., making appointments, requesting prescriptions, arranging transportation to appointments) were more likely to be engaged in adult care.<sup>55</sup> 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 care provider and an adult care provider to share joint care of a patient for a period of time.

Adolescent care providers should have a candid discussion with the transitioning adolescent and their caregivers to understand what qualities the adolescent considers most important when choosing an adult care setting (e.g., confidentiality, small clinic size, low patient-to-provider ratio, availability of after-school or evening appointments). Social determinants, such as the patient’s developmental status, behavioral/mental health co-morbidities, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration, should 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. **Recent studies have shown potential for successful transition and ongoing retention using models that include a multidisciplinary approach that utilizes internal medicine/pediatric-trained providers, peer navigators, social workers, mental health support, and a youth-focused care model for adolescents who were already attending adult HIV clinics.**<sup>56,57</sup> 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.<sup>15,52</sup> A report from the United Kingdom suggests that the mortality rate of adolescents with HIV increases after transition.<sup>20,53</sup> 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.<sup>51</sup> 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.<sup>2</sup> A recent retrospective study from Atlanta reported that, while retention rates were initially high when 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.<sup>53</sup>

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transition plans and who might benefit most from them.<sup>49,58-65</sup> To maximize the likelihood of success, providers should prepare adolescents for transition long before it occurs. Attention to the following key areas could improve retention in care and minimize the risk of ART interruptions:

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

## References

1. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr*. 2011;57(2):165-173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21407086>.
2. Xia Q, Shah D, Gill B, Torian LV, Braunstein SL. Continuum of care among people living with perinatally acquired HIV infection in New York City, 2014. *Public Health Rep*. 2016;131(4):566-573. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27453601>.

3. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. *J Int AIDS Soc.* 2013;16:18579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782477>.
4. Judd A, Lodwick R, Noguera-Julian A, et al. Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe. *HIV Med.* 2017;18(3):171-180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27625109>.
5. Bucek A, Leu CS, Benson S, et al. Psychiatric disorders, antiretroviral medication adherence, and viremia in a cohort of perinatally HIV-Infected adolescents and young adults. *Pediatr Infect Dis J.* 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29227462>.
6. Hermetet-Lindsay KD, Correia KF, Williams PL, et al. Contributions of disease severity, psychosocial factors, and cognition to behavioral functioning in US youth perinatally exposed to HIV. *AIDS Behav.* 2017;21(9):2703-2715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27475941>.
7. Tarantino N, Brown LK, Whiteley L, et al. Correlates of missed clinic visits among youth living with HIV. *AIDS Care.* 2018:1-8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29455553>.
8. Centers for Disease Control and Prevention. HIV surveillance report; vol. 29. 2018. Available at: <https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html>
9. Rakhmanina N, Phelps BR. Pharmacotherapy of pediatric HIV infection. *Pediatr Clin North Am.* 2012;59(5):1093-1115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23036246>.
10. Harris LL, Chernoff MC, Nichols SL, et al. Prospective memory in youth with perinatally-acquired HIV infection. *Child Neuropsychol.* 2018;24(7):938-958. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28782457>.
11. Bucek A, Leu CS, Benson S, et al. Psychiatric disorders, antiretroviral medication adherence and viremia in a cohort of perinatally HIV-infected adolescents and young adults. *Pediatr Infect Dis J.* 2018;37(7):673-677. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29227462>.
12. Mellins CA, Tassiopoulos K, Malee K, et al. Behavioral health risks in perinatally HIV-exposed youth: co-occurrence of sexual and drug use behavior, mental health problems, and nonadherence to antiretroviral treatment. *AIDS Patient Care STDS.* 2011;25(7):413-422. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21992620>.
13. Flynn PM, Rudy BJ, Lindsey JC, et al. Long-term observation of adolescents initiating HAART therapy: three-year follow-up. *AIDS Res Hum Retroviruses.* 2007;23(10):1208-1214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17961106>.
14. Hosek SG, Harper GW, Domanico R. Predictors of medication adherence among HIV-infected youth. *Psychol Health Med.* 2005;10(2):166-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25705113>.
15. Farmer C, Yehia BR, Fleishman JA, et al. Factors associated with retention among non-perinatally HIV-infected youth in the HIV research network. *J Pediatric Infect Dis Soc.* 2016;5(1):39-46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26908490>.
16. Mellins CA, Malee KM. Understanding the mental health of youth living with perinatal HIV infection: lessons learned and current challenges. *J Int AIDS Soc.* 2013;16:18593. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23782478>.
17. Mellins CA, Brackis-Cott E, Leu CS, et al. Rates and types of psychiatric disorders in perinatally human immunodeficiency virus-infected youth and seroreverters. *J Child Psychol Psychiatry.* 2009;50(9):1131-1138. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19298479>.
18. Gadow KD, Chernoff M, Williams PL, et al. Co-occurring psychiatric symptoms in children perinatally infected with HIV and peer comparison sample. *J Dev Behav Pediatr.* 2010;31(2):116-128. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20110828>.
19. Kapetanovic S, Wiegand RE, Dominguez K, et al. Associations of medically documented psychiatric diagnoses and risky health behaviors in highly active antiretroviral therapy-experienced perinatally HIV-infected youth. *AIDS Patient Care STDS.* 2011;25(8):493-501. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21745118>.
20. Fish R, Judd A, Jungmann E, O'Leary C, Foster C, HIV Young Persons Network. Mortality in perinatally HIV-infected

young people in England following transition to adult care: an HIV young persons network (HYPNet) audit. *HIV Med*. 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24112550>.

21. Kim SH, Gerver SM, Fidler S, Ward H. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. *AIDS*. 2014;28(13):1945-1956. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24845154>.
22. Chernoff M, Nachman S, Williams P, et al. Mental health treatment patterns in perinatally HIV-infected youth and controls. *Pediatrics*. 2009;124(2):627-636. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19596734>.
23. Sirois PA, Montepiedra G, Kapetanovic S, et al. Impact of medications prescribed for treatment of attention-deficit hyperactivity disorder on physical growth in children and adolescents with HIV. *J Dev Behav Pediatr*. 2009;30(5):403-412. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19827220>.
24. Funck-Brentano I, Dalban C, Veber F, et al. Evaluation of a peer support group therapy for HIV-infected adolescents. *AIDS*. 2005;19(14):1501-1508. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16135904>.
25. Brown LK, Kennard BD, Emslie GJ, et al. Effective treatment of depressive disorders in medical clinics for adolescents and young adults living with HIV: a controlled trial. *J Acquir Immune Defic Syndr*. 2016;71(1):38-46. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26761270>.
26. Benton TD, Kee Ng WY, Leung D, Canetti A, Karnik N. Depression among youth living with HIV/AIDS. *Child Adolesc Psychiatr Clin N Am*. 2019;28(3):447-459. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31076119>.
27. Knight JR, Shrier LA, Bravender TD, Farrell M, Vander Bilt J, Shaffer HJ. A new brief screen for adolescent substance abuse. *Arch Pediatr Adolesc Med*. 1999;153(6):591-596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10357299>.
28. Sultan B, White JA, Fish R, et al. The '3 in 1' study: pooling self-taken pharyngeal, urethral and rectal samples into a single sample for analysis, for diagnosis of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in men who have sex with men (MSM). *J Clin Microbiol*. 2015; 54(3):650-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26719439>.
29. Workowski KA, Bolan GA, Centers for Disease C, Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26042815>.
30. Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008–2011. *N Engl J Med*. 2016;374(9):843-852. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26962904>.
31. Sutton MY, Patel R, Frazier EL. Unplanned pregnancies among HIV-infected women in care-United States. *J Acquir Immune Defic Syndr*. 2014;65(3):350-358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24189153>.
32. Centers for Disease Control and Prevention. HIV surveillance report. 2018. Available at: <http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html>.
33. Marcell AV, Burstein GR, Committee On A. Sexual and reproductive health care services in the pediatric setting. *Pediatrics*. 2017;140(5). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29061870>.
34. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. 2019. Available at: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.
35. Sevinsky H, Eley T, Persson A, et al. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. *Antivir Ther*. 2011;16(2):149-156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21447863>.
36. Zhang J, Chung E, Yones C, et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. *Antivir Ther*. 2011;16(2):157-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21447864>.
37. El-Ibiary SY, Cocohoba JM. Effects of HIV antiretrovirals on the pharmacokinetics of hormonal contraceptives. *Eur J Contracept Reprod Health Care*. 2008;13(2):123-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18465473>.

38. Anderson MS, Hanley WD, Moreau AR, et al. Effect of raltegravir on estradiol and norgestimate plasma pharmacokinetics following oral contraceptive administration in healthy women. *Br J Clin Pharmacol*. 2011;71(4):616-620. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21395656>.
39. Kenny J, Williams B, Prime K, Tookey P, Foster C. Pregnancy outcomes in adolescents in the UK and Ireland growing up with HIV. *HIV Med*. 2012;13(5):304-308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22136754>.
40. Byrne L, Thorne C, Foster C, Tookey P. Pregnancy outcomes in women growing up with perinatally acquired HIV in the United Kingdom and Ireland. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25397443>.
41. Jao J, Agwu A, Mhango G, et al. Growth patterns in the first year of life differ in infants born to perinatally vs. nonperinatally HIV-infected women. *AIDS*. 2015;29(1):111-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25562495>.
42. Jao J, Sigel KM, Chen KT, et al. Small for gestational age birth outcomes in pregnant women with perinatally acquired HIV. *AIDS*. 2012;26(7):855-859. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22313958>.
43. Meloni A, Tuveri M, Florida M, et al. Pregnancy care in two adolescents perinatally infected with HIV. *AIDS Care*. 2009;21(6):796-798. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19806493>.
44. Williams SF, Keane-Tarchichi MH, Bettica L, Dieudonne A, Bardeguez AD. Pregnancy outcomes in young women with perinatally acquired human immunodeficiency virus-1. *Am J Obstet Gynecol*. 2009;200(2):149 e141-145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18973871>.
45. Cruz ML, Cardoso CA, Joao EC, et al. Pregnancy in HIV vertically infected adolescents and young women: a new generation of HIV-exposed infants. *AIDS*. 2010;24(17):2727-2731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20827164>.
46. Elgalib A, Hegazi A, Samarawickrama A, et al. Pregnancy in HIV-infected teenagers in London. *HIV Med*. 2011;12(2):118-123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20807252>.
47. Calitri C, Gabiano C, Galli L, et al. The second generation of HIV-1 vertically exposed infants: a case series from the Italian register for paediatric HIV infection. *BMC Infect Dis*. 2014;14:277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24885649>.
48. Tepper V, Zaner S, Ryscavage P. HIV healthcare transition outcomes among youth in North America and Europe: a review. *J Int AIDS Soc*. 2017;20(Suppl 3):60-70. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28530041>.
49. Judd A, Davies MA. Adolescent transition among young people with perinatal HIV in high-income and low-income settings. *Curr Opin HIV AIDS*. 2018;13(3):236-248. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29528851>.
50. Foster C, Fidler S. Optimizing HIV transition services for young adults. *Curr Opin Infect Dis*. 2018;31(1):33-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29210712>.
51. Ryscavage P, Macharia T, Patel D, Palmeiro R, Tepper V. Linkage to and retention in care following healthcare transition from pediatric to adult HIV care. *AIDS Care*. 2016;28(5):561-565. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26766017>.
52. Tanner AE, Philbin MM, Chambers BD, et al. Healthcare transition for youth living with HIV: outcomes from a prospective multi-site study. *J Adolesc Health*. 2018;63(2):157-165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29887488>.
53. Hussen SA, Chakraborty R, Knezevic A, et al. Transitioning young adults from paediatric to adult care and the HIV care continuum in Atlanta, Georgia, USA: a retrospective cohort study. *J Int AIDS Soc*. 2017;20(1):1-9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28872281>.
54. Reiss JG, Gibson RW, Walker LR. Health care transition: youth, family, and provider perspectives. *Pediatrics*. 2005;115(1):112-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15629990>.
55. Tassiopoulos K, Huo Y, Patel K, et al. Ability to manage health after transition to adult care is associated with retention in care among young adults with perinatal HIV infection. Presented at: International AIDS Conference. 2018.

Amsterdam, Netherlands. Available at: <http://programme.aids2018.org/Abstract/Abstract/2533>.

56. Griffith D, Jin L, Childs J, Posada R, Jao J, Agwu A. Outcomes of a comprehensive retention strategy for youth with HIV after transfer to adult care in the United States. *Pediatr Infect Dis J*. 2019;38(7):722-726. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30985513>.
57. Griffith D, Snyder J, Dell S, Nolan K, Keruly J, Agwu A. Impact of a youth-focused care model on retention and virologic suppression among young adults with HIV cared for in an Adult HIV Clinic. *J Acquir Immune Defic Syndr*. 2019;80(2):e41-e47. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30422910>.
58. Rosen DS, Blum RW, Britto M, Sawyer SM, Siegel DM, Society for adolescent M. transition to adult health care for adolescents and young adults with chronic conditions: position paper of the society for adolescent medicine. *J Adolesc Health*. 2003;33(4):309-311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14519573>.
59. Gilliam PP, Ellen JM, Leonard L, Kinsman S, Jevitt CM, Straub DM. Transition of adolescents with HIV to adult care: characteristics and current practices of the adolescent trials network for HIV/AIDS interventions. *J Assoc Nurses AIDS Care*. 2011;22(4):283-294. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20541443>.
60. New York State Department of Health AIDS Institute. Transitioning HIV-infected adolescents into adult care. 2011.
61. Andiman WA. Transition from pediatric to adult healthcare services for young adults with chronic illnesses: the special case of human immunodeficiency virus infection. *J Pediatr*. 2011;159(5):714-719. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21868035>.
62. Dowshen N, D'Angelo L. Health care transition for youth living with HIV/AIDS. *Pediatrics*. 2011;128(4):762-771. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21930548>.
63. Committee On Pediatric AIDS. Transitioning HIV-infected youth into adult health care. *Pediatrics*. 2013;132(1):192-197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23796739>.
64. Sharer M, Fullem A. Transitioning of care and other services for adolescents living with HIV in Sub-Saharan Africa. Arlington, VA: USAID's AIDS Support and Technical Assistance Resources, AIDSTAR-One, Task Order 1. 2012.
65. Hussen SA, Chahroudi A, Boylan A, Camacho-Gonzalez AF, Hackett S, Chakraborty R. Transition of youth living with HIV from pediatric to adult-oriented healthcare: a review of the literature. *Future Virol*. 2015;9(10):921-929. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25983853>.

# Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV (Last updated April 14, 2020; last reviewed April 14, 2020)

## Panel's Recommendations

- Strategies to maximize adherence should be discussed **before and/or at initiation** of antiretroviral therapy (ART) and again before changing regimens **(AIII)**.
- Adherence to therapy must be assessed and promoted at each visit, and strategies to maintain and/or improve adherence must be continually explored **(AIII)**.
- In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used **(AIII)**.
- Once-daily antiretroviral regimens and regimens with a low pill burden should be prescribed whenever feasible **(AII\*)**.

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

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

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

## Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression. Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, and subtherapeutic or partial dosing.<sup>1,2</sup> Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of 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.<sup>3</sup> 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; it can also 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.<sup>4-6</sup> Several studies have demonstrated that adherence is not static and can vary with time on treatment.<sup>7</sup> **More recently, findings from the U.S. Pediatric AIDS/HIV Cohort Study (PHACS) demonstrated that the prevalence of nonadherence increased with age. Among 381 children and adolescents with perinatal HIV infection, the prevalence of nonadherence increased from 31% to 50% ( $P < 0.001$ ) and the prevalence of unsuppressed viral loads increased from 16% to 40% ( $P < 0.001$ ) between pre-adolescence and late adolescence/young adulthood.**<sup>8</sup> 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.<sup>9,10</sup> **Despite improvements over the last several years, the** limited availability of once-daily and single-tablet regimens and palatable formulations for infants and young

children remains especially problematic.<sup>11</sup> Furthermore, infants and children are dependent on others for medication administration; adult caregivers may face barriers that contribute to nonadherence in children, including forgetting doses, changes in routine, being too busy, and child refusal.<sup>12,13</sup> Some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.<sup>14</sup> 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, violence, involvement with the criminal justice system, limited social support).<sup>15,16</sup>

## Adherence Assessment and Monitoring

Clinicians should begin assessing potential barriers to adherence and discussing the importance of adherence with patients before initiating or changing an ARV regimen. Evaluations should assess social and behavioral factors that may influence adherence and should identify individual needs for intervention. Clinicians should ask patients about their experience with taking medications, as well as concerns and expectations about treatment. Before beginning treatment, it is important that the patient explicitly agrees to the treatment plan, which should include 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.<sup>17-19</sup> Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals who are on ART (see [Plasma HIV-1 RNA \[Viral Load\] and CD4 Count Monitoring](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). In addition, it can be used as positive reinforcement to encourage continued adherence.<sup>20</sup> Clinicians should use at least one other method to assess adherence in addition to monitoring viral load.<sup>18</sup> Table 13 includes common approaches to monitoring medication adherence.

## Strategies to Improve and Support Adherence

When 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 (or a regimen change)**, 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. 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.<sup>21</sup>

### *Regimen-Related Strategies*

**ARV regimens for infants and young children often require taking multiple daily doses of multiple pills or liquids, some of which are unpalatable and each of which has the potential for adverse effects (AEs) and drug interactions. 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 drugs in the regimen should be chosen to minimize drug interactions and AEs.<sup>22</sup> Efforts should be made to reduce the pill burden and pill size and to prescribe once-daily ARV regimens and single-tablet regimens whenever feasible (see Table 16 in [Management of Children Receiving Antiretroviral Therapy](#)). With the introduction of new 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 for less toxic, simplified regimens, particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-daily ARV regimens than with twice-daily regimens, and better adherence with single-tablet formulations than with multiple-tablet regimens.<sup>11,23-26</sup> [Appendix A, Table 1](#) shows which ARV drugs are available in fixed-dose combination (FDC) tablets, and [Appendix A, Table 2](#) provides information about minimum body weight requirements and other considerations when using FDC tablets in children.

When nonadherence is related to the poor palatability of a liquid formulation or crushed pills, the offending taste can sometimes be masked with a small amount of flavoring syrup or food if simultaneous administration of food is not contraindicated (see [Appendix A: Pediatric Antiretroviral Drug Information](#)).<sup>27</sup> Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children and youth aged 4 years to 21 years found that training children to swallow pills was associated with improved adherence at 6 months post-training.<sup>28</sup> Finally, if drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs by changing the particular drug (or, if necessary, the drug regimen) when feasible.

### ***Patient/Family-Related Strategies***

Patient and caregiver education is an essential component of establishing good medication adherence in children. Educating families about adherence should begin before initiating or changing ARV medications and should include a discussion of the goals of therapy, the importance of optimizing adherence, and the specific plans for supporting and maintaining a child's medication adherence. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes. Additionally, it may be helpful to assess the medication adherence of the caregiver or other household members who currently take ARV drugs or other chronic medications.

Several behavioral tools can be used to integrate taking medications into a child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives (including financial incentives) for taking medications, can be effective tools to promote adherence.<sup>29</sup> Treating mental health disorders (e.g., depression) may facilitate adherence to complex ARV regimens.<sup>30,31</sup>

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.<sup>32</sup> 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, the use of a gastrostomy tube may be considered.<sup>33</sup> If adequate resources are available, home-nursing interventions or directly observed therapy (DOT) may also be beneficial. **The evidence is mixed as to the efficacy of programs that are designed to improve adherence** through DOT, but DOT may still be a useful strategy for some patients.<sup>34-36</sup>

Other strategies to support adherence include using 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](#).

**A recent systematic review of studies that evaluated the use of mobile phone technologies to improve ART adherence concluded that the use of mobile short message service (SMS) interventions improved adherence to ART compared with control conditions. A recent systematic review of studies that evaluated the use of mobile**

phone technologies to improve ART adherence reported mixed results; the efficacy of SMS interventions varied depending on the specific SMS intervention tested.<sup>37</sup> Another recent systematic review of the effectiveness of using mobile phone interventions to improve adherence to ART also reported mixed results; effectiveness varied depending on the measured outcomes and the specific intervention (e.g., whether the study evaluated the use of texts or the use of phone calls).<sup>38</sup> 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.<sup>39-44</sup>

### 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. Approaches for Monitoring Medication Adherence**

<b>Routine Assessment of Medication Adherence in Clinical Care<sup>a</sup></b>	<b>Description</b>
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications. <sup>a</sup>
Assess a quantitative self-report of missed doses.	Ask the patient and/or caregiver about the number of missed doses over a defined period (1, 3, or 7 days).
Request a description of the medication regimen.	Ask the patient and/or caregiver about the name, appearance, and number of medications, and how often the medications are taken.
Assess barriers to medication administration.	Engage the patient and caregiver in a dialogue about potential barriers to adherence and strategies to overcome them.
Monitor pharmacy refills.	Approaches include a pharmacy-based or clinic-based assessment of on-time medication refills.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to the clinic, home visits, or referral to community health nursing.
<b>Targeted Approaches to Monitoring Adherence in Special Circumstances</b>	<b>Description</b>
Implement DOT.	Include a brief period of hospitalization if indicated.
Measure drug concentration in plasma <b>or DBS</b> .	Measuring drug concentrations can be considered for particular drugs.
<b>Approaches to Monitoring Medication Adherence in Research Settings</b>	<b>Description</b>
Measure drug concentrations in hair.	<b>Measuring hair drug concentrations can be considered for particular drugs; it provides a good measure of adherence over time.</b> <sup>17,45,46</sup>
Use electronic monitoring devices.	Approaches include MEMS caps and Wisepill.
Use cell phone-based technologies.	Approaches include interactive voice response, text messaging, and mobile apps.

<sup>a</sup> See [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#) regarding the frequency of adherence assessment after initiating or changing therapy.

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

**Table 14. Strategies to Improve Adherence to Antiretroviral Medications**

Initial Intervention Strategies
<ul style="list-style-type: none"> <li>• Establish trust and identify mutually acceptable goals for care.</li> <li>• Obtain explicit agreement on the need for treatment and adherence.</li> <li>• 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.</li> <li>• <b>Determine whether the child is aware of their HIV status. Consider talking to the child's caregivers about disclosing this information to the child in a developmentally appropriate way.</b></li> <li>• Identify family, friends, health team members, and others who can support adherence.</li> <li>• 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.</li> <li>• Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them in arranging administration during day care, school, and in other settings, when needed. Consider home delivery of medications.</li> <li>• Establish a patient's readiness to take medication by staging practice sessions or by other means.</li> <li>• Schedule a home visit to review medications and determine how they will be administered in the home setting.</li> <li>• 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.</li> </ul>
Medication Strategies
<ul style="list-style-type: none"> <li>• Choose the simplest regimen possible; reduce dosing frequency, pill size, and number of pills (see <a href="#">Appendix A, Table 1</a> and <a href="#">Appendix A, Table 2</a>).</li> <li>• When choosing a regimen, consider the patient's daily and weekly routines and potential variations in patient and family activities.</li> <li>• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).</li> <li>• Choose drugs with the fewest AEs; provide anticipatory guidance for managing AEs.</li> <li>• Simplify food requirements for medication administration.</li> <li>• Prescribe drugs carefully to avoid adverse drug-drug interactions.</li> <li>• Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.</li> </ul>
Follow-Up Intervention Strategies
<ul style="list-style-type: none"> <li>• 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.</li> <li>• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.</li> <li>• Use patient education aids, including pictures, calendars, and stickers.</li> <li>• Encourage the use of pill boxes, reminders, mobile apps, alarms, and timers.</li> <li>• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.</li> <li>• 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.</li> <li>• Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.</li> <li>• Consider DOT at home, in the clinic, or, in certain circumstances, during a brief period of inpatient hospitalization.</li> <li>• Consider gastrostomy tube use in certain circumstances.</li> <li>• Information on other interventions to consider can be found at the <a href="#">Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions</a> on CDC's website.</li> <li>• Consult the CDC <a href="#">Every Dose Every Day toolkit</a>.</li> </ul>

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

## References

1. Vreeman RC, Nyandiko WM, Liu H, et al. Measuring adherence to antiretroviral therapy in children and adolescents in western Kenya. *J Int AIDS Soc.* 2014;17:19227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25427633>.
2. Hawkins A, Evangeli M, Sturgeon K, Le Prevost M, Judd A, Aalphi Steering Committee. Episodic medication adherence in adolescents and young adults with perinatally acquired HIV: a within-participants approach. *AIDS Care.* 2016;28 Suppl 1:68-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26886514>.
3. Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS.* 2009;23(9):1035-1046. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19381075>.
4. MacDonell KK, Jacques-Tiura AJ, Naar S, Fernandez MI, ATNP 086/106 Protocol Team. Predictors of self-reported adherence to antiretroviral medication in a multisite study of ethnic and racial minority HIV-positive youth. *J Pediatr Psychol.* 2016;41(4):419-428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26498724>.
5. Gray ME, Nieburg P, Dillingham R. Pediatric human immunodeficiency virus continuum of care: a concise review of evidence-based practice. *Pediatr Clin North Am.* 2017;64(4):879-891. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28734516>.
6. Schlatter AF, Deathe AR, Vreeman RC. The need for pediatric formulations to treat children with HIV. *AIDS Res Treat.* 2016;2016:1654938. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27413548>.
7. Giannattasio A, Albano F, Giacomet V, Guarino A. The changing pattern of adherence to antiretroviral therapy assessed at two time points, 12 months apart, in a cohort of HIV-infected children. *Expert Opin Pharmacother.* 2009;10(17):2773-2778. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19929700>.
8. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among US youth with perinatally acquired HIV. *AIDS.* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31274538>.
9. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep.* 2009;6(4):194-200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19849962>.
10. Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. *PLoS Med.* 2016;13(11):e1002183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27898679>.
11. Clay PG, Nag S, Graham CM, Narayanan S. Meta-analysis of studies comparing single and multi-tablet fixed dose combination HIV treatment regimens. *Medicine (Baltimore).* 2015;94(42):e1677. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26496277>.
12. Marhefka SL, Koenig LJ, Allison S, et al. Family experiences with pediatric antiretroviral therapy: responsibilities, barriers, and strategies for remembering medications. *AIDS Patient Care STDS.* 2008;22(8):637-647. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18627275>.
13. Skovdal M, Campbell C, Madanhire C, Nyamukapa C, Gregson S. Challenges faced by elderly guardians in sustaining the adherence to antiretroviral therapy in HIV-infected children in Zimbabwe. *AIDS Care.* 2011;23(8):957-964. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21400306>.
14. Naar-King S, Montepiedra G, Nichols S, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol.* 2009;34(2):187-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18586756>.
15. Cluver LD, Hodes RJ, Toska E, et al. 'HIV is like a tsotsi. ARVs are your guns': associations between HIV-disclosure and adherence to antiretroviral treatment among adolescents in South Africa. *AIDS.* 2015;29 Suppl 1:S57-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26049539>.
16. Cluver L, Meinck F, Toska E, Orkin FM, Hodes R, Sherr L. Multitype violence exposures and adolescent antiretroviral nonadherence in South Africa. *AIDS.* 2018;32(8):975-983. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29547438>.
17. Pintye J, Bacchetti P, Teeraananchai S, et al. Brief report: lopinavir hair concentrations are the strongest predictor of viremia in HIV-infected Asian children and adolescents on second-line antiretroviral therapy. *J Acquir Immune Defic*

Syndr. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28825944>.

18. Al-Hassany L, Kloosterboer SM, Dierckx B, Koch BC. Assessing methods of measuring medication adherence in chronically ill children—a narrative review. *Patient Prefer Adherence*. 2019;13:1175-1189. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31413546>.
19. Craker L, Tarantino N, Whiteley L, Brown L. Measuring antiretroviral adherence among young people living with HIV: observations from a real-time monitoring device versus self-report. *AIDS Behav*. 2019;23(8):2138-2145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30888573>.
20. Bonner K, Mezochow A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *J Acquir Immune Defic Syndr*. 2013;64(1):74-78. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23774877>.
21. Centers for Disease Control and Prevention. Medication adherence. 2014.
22. Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care STDS*. 2009;23(10):803-807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19795999>.
23. Nacheha JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2014;58(9):1297-1307. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24457345>.
24. Pantuzza LL, Ceccato M, Silveira MR, Junqueira LMR, Reis AMM. Association between medication regimen complexity and pharmacotherapy adherence: a systematic review. *Eur J Clin Pharmacol*. 2017;73(11):1475-1489. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28779460>.
25. Griffith DC, Farmer C, Gebo KA, et al. Uptake and virological outcomes of single- versus multi-tablet antiretroviral regimens among treatment-naive youth in the HIV research network. *HIV Med*. 2019;20(2):169-174. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30561888>.
26. Altice F, Evuarherhe O, Shina S, Carter G, Beaubrun AC. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient Prefer Adherence*. 2019;13:475-490. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31040651>.
27. Czyzewski D, Runyan D, Lopez M, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader*. 2000;10(2):88-95. Available at: <https://researchers.dellmed.utexas.edu/en/publications/teaching-and-maintaining-pill-swallowing-in-hiv-infected-children>.
28. Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics*. 2007;119(4):e893-899. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17353298>.
29. Foster C, McDonald S, Frize G, Ayers S, Fidler S. “Payment by Results”—financial incentives and motivational interviewing, adherence interventions in young adults with perinatally acquired HIV-1 infection: a pilot program. *AIDS Patient Care STDS*. 2014;28(1):28-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24428797>.
30. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Ann Behav Med*. 2014;47(3):259-269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24234601>.
31. Bucek A, Leu CS, Benson S, et al. Psychiatric disorders, antiretroviral medication adherence and viremia in a cohort of perinatally HIV-infected adolescents and young adults. *Pediatr Infect Dis J*. 2018;37(7):673-677. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29227462>.
32. Nichols J, Steinmetz A, Paintsil E. Impact of HIV-status disclosure on adherence to antiretroviral therapy among HIV-infected children in resource-limited settings: a systematic review. *AIDS Behav*. 2017;21(1):59-69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27395433>.
33. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics*. 2000;105(6):E80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10835093>.
34. Bain-Brickley D, Butler LM, Kennedy GE, Rutherford GW. Interventions to improve adherence to antiretroviral therapy in children with HIV infection. *Cochrane Database Syst Rev*. 2011;12(12):CD009513. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22161452>.

35. Gaur AH, Belzer M, Britto P, et al. Directly observed therapy (DOT) for nonadherent HIV-infected youth: lessons learned, challenges ahead. *AIDS Res Hum Retroviruses*. 2010;26(9):947-953. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20707731>.
36. Hart JE, Jeon CY, Ivers LC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. *J Acquir Immune Defic Syndr*. 2010;54(2):167-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20375848>.
37. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. *PLoS One*. 2018;13(9):e0204091. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30240417>.
38. Shah R, Watson J, Free C. A systematic review and meta-analysis in the effectiveness of mobile phone interventions used to improve adherence to antiretroviral therapy in HIV infection. *BMC Public Health*. 2019;19(1):915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31288772>.
39. Shaw S, Amico KR. Antiretroviral therapy adherence enhancing interventions for adolescents and young adults 13-24 Years of Age: a review of the evidence base. *J Acquir Immune Defic Syndr*. 2016;72(4):387-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26959190>.
40. Judd A, Sohn AH, Collins IJ. Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care: moving on up. *Curr Opin HIV AIDS*. 2016;11(5):477-486. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27272537>.
41. MacPherson P, Munthali C, Ferguson J, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. *Trop Med Int Health*. 2015;20(8):1015-1032. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25877007>.
42. Kanters S, Park JJ, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV*. 2017;4(1):e31-e40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27863996>.
43. Camacho-Gonzalez AF, Gillespie SE, Thomas-Seaton L, et al. The metropolitan atlanta community adolescent rapid testing initiative study: closing the gaps in HIV care among youth in Atlanta, Georgia, USA. *AIDS*. 2017;31 Suppl 3:S267-S275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28665885>.
44. Casale M, Carlqvist A, Cluver L. Recent interventions to improve retention in HIV Care and adherence to antiretroviral treatment among adolescents and youth: a systematic review. *AIDS Patient Care STDS*. 2019;33(6):237-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31166783>.
45. Olds PK, Kiwanuka JP, Nansera D, et al. Assessment of HIV antiretroviral therapy adherence by measuring drug concentrations in hair among children in rural Uganda. *AIDS Care*. 2015;27(3):327-332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25483955>.
46. Chawana TD, Gandhi M, Nathoo K, et al. Defining a cutoff for atazanavir in hair samples associated with virological failure among adolescents failing second-line antiretroviral treatment. *J Acquir Immune Defic Syndr*. 2017;76(1):55-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28520618>.

# Management of Medication Toxicity or Intolerance (Last updated April 14, 2020; last reviewed April 14, 2020)

## 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; an agent with a different toxicity and side-effect profile should be chosen (**AI\***).
- The toxicity and the medication presumed to be 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 recommended** 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

Effective antiretroviral therapy (ART) results in viral suppression and improved immune function. These benefits 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](#)).<sup>1</sup> In recent clinical trials with newer ARV drugs, however, <10% of ARV-treated patients had treatment-limiting AEs.<sup>2-9</sup>

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.<sup>2,4,5,10-13</sup> **Unexpected AEs may emerge with additional clinical experience with newer ARV drugs. The prevalence and the relationship of these AEs to newer ARV drugs can be unclear (e.g., weight gain with the use of integrase strand transfer inhibitors [INSTIs]; see [Table 15h](#)).**<sup>14,15</sup> To achieve sustained viral suppression throughout 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 history of drug intolerance or viral resistance.

The AEs caused by ARV drugs can vary from mild, more common symptoms (e.g., gastrointestinal [GI] 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 (ABC) hypersensitivity.<sup>16</sup> For certain children aged <3 years who require treatment with efavirenz (EFV), an additional pharmacogenetic marker, cytochrome P450 2B6 genotype, should be assessed in an attempt to prevent toxicity (see the [Efavirenz](#)

section in Appendix A: Pediatric Antiretroviral Drug Information).<sup>16-20</sup>

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 include selected references that provide further information about these toxicities in pediatric patients.

As new ARV drugs are approved for use in children, many of the older ARV drugs **are no longer recommended** because they have unacceptable toxicities, inferior virologic efficacy, a high pill burden, pharmacologic concerns, and/or a limited amount of pediatric data. The following older ARV drugs have therefore been removed from the Management of Medication Toxicity or Intolerance tables:

- Didanosine (ddI)
- Enfuvirtide
- Fosamprenavir
- Indinavir
- Nelfinavir
- Saquinavir
- Stavudine (d4T)
- 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., ddI, d4T), 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., a hypersensitivity reaction [HSR] to ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV drugs and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life threatening (e.g., urolithiasis caused by atazanavir, renal tubulopathy caused by tenofovir disoproxil fumarate) 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 suspected 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 drug 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 GI 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. Central nervous system (CNS) AEs are commonly encountered when initiating therapy with EFV. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take EFV-containing regimens at bedtime and on an empty stomach to help minimize these AEs. Patients should be advised that these AEs usually diminish within 2 to 4 weeks of initiating therapy in most people; however, they may persist for months in some patients, and may require a medication change.<sup>21,22</sup> 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.<sup>23,24</sup>

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.<sup>7,25,26</sup> For mild to moderate toxicities, changing to a drug with a different toxicity profile may be sufficient; discontinuing 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 reverse transcriptase inhibitor backbone, due to the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., HSR—see [Table 15k](#)) should stop all components of the drug regimen simultaneously, regardless of drug half-life. Once the cause of the AE has been determined, clinicians can either initiate a new ARV regimen that does not contain the offending drug or resume 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 an ARV regimen 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.<sup>27-30</sup> 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. Therapeutic drug monitoring (TDM) is not routinely recommended; however, it may be used in cases where mild or moderate toxicity is thought to be the result of a drug concentration exceeding the normal therapeutic range.<sup>31,32</sup> An expert in the management of pediatric HIV should be consulted when dose reduction is being considered based on the results of TDM. Dose reduction after TDM has been studied most extensively with EFV, since increased CNS toxicity has clearly been associated with higher levels of EFV (see the [Efavirenz](#) section 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., switching to ABC for zidovudine-related anemia or to a PI or INSTI for EFV-related CNS symptoms).
- Using dose reduction, guided by TDM, after consulting with an expert in pediatric HIV.

## References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2019. Available at: <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>.
2. Arpadi S, Shiao S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child*. 2013;98(4):258-264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23220209>.
3. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23473847>.
4. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc*. 2013;16:18600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782481>.
5. Purswani M, Patel K, Kopp JB, et al. Tenofovir treatment duration predicts proteinuria in a multiethnic United States cohort of children and adolescents with perinatal HIV-1 infection. *Pediatr Infect Dis J*. 2013;32(5):495-500. Available

at: <http://www.ncbi.nlm.nih.gov/pubmed/23249917>.

6. Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS*. 2013;27(9):1403-1412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23343913>.
7. Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PLoS One*. 2017;12(2):e0169762. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28192529>.
8. Viani RM, Alvero C, Fenton T, et al. Safety, Pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatr Infect Dis J*. 2015;34(11):1207-13. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26244832>.
9. Nachman S, Alvero C, Teppler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a Phase 1/2 open label, non-randomised, multicentre trial. *Lancet HIV*. 2018;5(12):e715-e722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30527329>.
10. Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *J Virus Erad*. 2018;4(2):72-79. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29682298>.
11. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. *Lancet HIV*. 2018;5(6):e291-e300. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29731407>.
12. Arrive E, Viard JP, Salanave B, et al. Metabolic risk factors in young adults infected with HIV since childhood compared with the general population. *PLoS One*. 2018;13(11):e0206745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30408056>.
13. Dona D, Mozzo E, Luise D, et al. Impact of HIV-1 infection and antiretroviral therapy on bone homeostasis and mineral density in vertically infected patients. *J Osteoporos*. 2019:1279318. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30693083>.
14. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis*. 2019;pii:ciz407. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31100116>.
15. Norwood J, Turner M, Bofill C, et al. Brief report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr*. 2017;76(5):527-531. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28825943>.
16. Asensi V, Collazos J, Valle-Garay E. Can antiretroviral therapy be tailored to each human immunodeficiency virus-infected individual? Role of pharmacogenomics. *World J Virol*. 2015;4(3):169-177. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26279978>.
17. Sinxadi PZ, Leger PD, McIlleron HM, et al. Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. *Br J Clin Pharmacol*. 2015;80(1):146-156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25611810>.
18. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. *AIDS*. 2017;31(8):1129-1136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28323755>.
19. Gallien S, Journot V, Loriot MA, et al. Cytochrome 2B6 polymorphism and efavirenz-induced central nervous system symptoms : a substudy of the ANRS ALIZE trial. *HIV Med*. 2017;18(8):537-545.; Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28145050>.
20. Soeria-Atmadja S, Osterberg E, Gustafsson LL, et al. Genetic variants in CYP2B6 and CYP2A6 explain interindividual variation in efavirenz plasma concentrations of HIV-infected children with diverse ethnic origin. *PLoS One*. 2017;12(9):e0181316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28886044>.
21. Gazzard B, Duvivier C, Zagler C, et al. Phase 2 double-blind, randomized trial of etravirine versus efavirenz in

- treatment-naïve patients: 48-week results. *AIDS*. 2011;25(18):2249-2258. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21881478>.
22. Wynberg E, Williams E, Tudor-Williams G, Lyall H, Foster C. Discontinuation of efavirenz in paediatric patients: why do children switch? *Clin Drug Investig*. 2018;38(3):231-238. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29181714>.
23. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among US youth with perinatally acquired HIV. *AIDS*. 2019;33(12):1923-1934 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31274538>.
24. Swan H, Reisman JI, McDannold SE, Glickman ME, McInnes DK, Gifford AL. The relationship between gastrointestinal symptom attribution, bothersomeness, and antiretroviral adherence among adults with HIV. *AIDS Care*. 2018;30(8):997-1003. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29415554>.
25. Davidson I, Beardsell H, Smith B, et al. The frequency and reasons for antiretroviral switching with specific antiretroviral associations: the SWITCH study. *Antiviral Res*. 2010;86(2):227-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20211651>.
26. Strehlau R, Shiao S, Arpadi S, et al. Substituting abacavir for stavudine in children who are virally suppressed without Lipodystrophy: Randomized Clinical Trial in Johannesburg, South Africa. *J Pediatric Infect Dis Soc*. 2018;7(3):e70-e77. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29373687>.
27. Valantin MA, Bittar R, de Truchis P, et al. Switching the nucleoside reverse transcriptase inhibitor backbone to tenofovir disoproxil fumarate + emtricitabine promptly improves triglycerides and low-density lipoprotein cholesterol in dyslipidaemic patients. *J Antimicrob Chemother*. 2010;65(3):556-561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20053692>.
28. Murnane PM, Strehlau R, Shiao S, et al. Switching to efavirenz versus remaining on ritonavir-boosted lopinavir in HIV-infected children exposed to nevirapine: long-term outcomes of a randomized trial. *Clin Infect Dis*. 2017;13(11):e0206745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28419200>.
29. Raffi F, Esser S, Nunnari G, Perez-Valero I, Waters L. Switching regimens in virologically suppressed HIV-1-infected patients: evidence base and rationale for integrase strand transfer inhibitor (INSTI)-containing regimens. *HIV Med*. 2016;17 Suppl 5:3-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27714978>.
30. Jao J, Yu W, Patel K, et al. Improvement in lipids after switch to boosted atazanavir or darunavir in children/adolescents with perinatally acquired HIV on older protease inhibitors: results from the Pediatric HIV/AIDS Cohort Study. *HIV Med*. 2018;19(3):175-183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29159965>.
31. Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit*. 2011;33(3):265-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21566505>.
32. Vo TT, Varghese Gupta S. Role of cytochrome P450 2B6 pharmacogenomics in determining efavirenz-mediated central nervous system toxicity, treatment outcomes, and dosage adjustments in patients with human immunodeficiency virus infection. *Pharmacotherapy*. 2016;36(12):1245-1254. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27779789>.

**Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Global CNS Depression</b>	LPV/r oral solution (contains both ethanol and propylene glycol as excipients)	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>1–6 days after starting LPV/r</li> </ul> <p><b>Presentation</b></p> <p><i>Neonates/Premature Infants:</i></p> <ul style="list-style-type: none"> <li>Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence)</li> </ul>	Unknown; rare case reports have been published	<p>Prematurity</p> <p>Low birth weight</p> <p>Aged &lt;14 days (whether birth was premature or term)</p>	<p>Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age of ≥14 days unless no other alternatives are available, <a href="#">see Lopinavir/Ritonavir</a>.</p>	<p>Discontinue LPV/r; symptoms should resolve in 1–5 days.</p> <p>If needed, reintroduction of LPV/r can be considered once the patient is outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).</p>
<b>Neuropsychiatric Symptoms and Other CNS Manifestations</b>	EFV	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>For many symptoms, onset is 1–2 days after starting EFV.</li> <li>Many symptoms subside or diminish by 2–4 weeks, but symptoms may persist in a significant proportion of patients.</li> </ul> <p><b>Presentation (May Include One or More of the Following)</b></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> <li>Abnormal dreams</li> <li>Psychosis</li> <li>Suicidal ideation or attempted/completed suicide</li> </ul> <p><i>Other CNS Manifestations:</i></p> <ul style="list-style-type: none"> <li>Dizziness</li> <li>Somnolence</li> <li>Insomnia or poor sleep quality</li> <li>Impaired concentration</li> <li>Seizures (including absence seizures)</li> <li>Cerebellar dysfunction (e.g., tremor, dysmetria, ataxia)</li> </ul> <p><b>Note:</b> CNS side effects (e.g., impaired concentration, abnormal dreams, sleep disturbances) may be more difficult to assess in children.</p>	<p>Variable, depending on age, symptoms, and assessment method</p> <p><b>Children:</b></p> <ul style="list-style-type: none"> <li>24% of patients experienced any EFV-related CNS manifestation in one case series, with 18% of participants requiring drug discontinuation.</li> <li>Five of 45 participants (11%) experienced new-onset seizures in one study of children aged &lt;36 months; two of these participants had alternative causes for seizures.</li> <li>Cases of cerebellar dysfunction have been reported in children with very high EFV plasma levels.</li> </ul> <p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>30% incidence for any CNS manifestations of any severity.</li> <li>6% incidence for EFV-related, severe CNS manifestations, including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality.</li> <li>One case series reported 20 women with ataxia that resolved upon EFV discontinuation, but frequency was not reported.</li> </ul>	<p>Insomnia is associated with elevated EFV trough concentration (≥4 mcg/mL)</p> <p>CYP2B6 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 T/T genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants)</p> <p>History of psychiatric illness or use of psychoactive drugs</p>	<p>Administer EFV on an empty stomach, preferably at bedtime.</p> <p>Prescreen for psychiatric illness; avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs.</p> <p>Consider using TDM in children with mild or moderate EFV-associated toxicities.</p>	<p>If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration is &gt;4 mcg/mL and/or symptoms are severe, strongly consider drug substitution if a suitable alternative exists.</p> <p>Alternatively, consider dose reduction with repeat TDM and dose adjustment (with input from an expert pharmacologist).</p>

**Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	RPV	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Most symptoms occur in the first 4–8 weeks of treatment.</li> </ul> <p><b>Presentation</b></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> <li>• Depressive disorders</li> <li>• Suicidal ideation</li> <li>• Abnormal dreams/nightmares</li> </ul> <p><i>Other CNS Manifestations:</i></p> <ul style="list-style-type: none"> <li>• Headache</li> <li>• Dizziness</li> <li>• Insomnia</li> <li>• Somnolence</li> </ul>	<p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>• CNS/neuro-psychiatric adverse events of all severity grades were reported in 43% of patients at 96 weeks (most were Grade 1). Depressive disorders of all severity grades were reported in 9% of patients; 1% of patients discontinued RPV due to severe depressive disorders.</li> </ul> <p><b>Children:</b></p> <ul style="list-style-type: none"> <li>• Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12–17 years. Severe depressive disorders were reported in 5.6% of patients, including one suicide attempt.</li> <li>• Somnolence was reported in five of 36 children (14%).</li> </ul>	History of neuropsychiatric illness	Monitor carefully for depressive disorders and other CNS symptoms.	Consider drug substitution in cases of severe symptoms.
	RAL	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• As early as 3–4 days after starting RAL</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Increased psychomotor activity</li> <li>• Headaches</li> <li>• Insomnia</li> <li>• Depression</li> <li>• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia)</li> </ul>	<p><b>Children:</b></p> <ul style="list-style-type: none"> <li>• Increased psychomotor activity was reported in one child.</li> </ul> <p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>• Headache</li> <li>• Insomnia (&lt;5% in adult trials)</li> <li>• Rare case reports of cerebellar dysfunction in adults</li> </ul>	<p>Elevated RAL concentrations</p> <p>Co-treatment with TDF, a PPI, or inhibitors of UGT1A1</p> <p>Prior history of insomnia or depression</p>	<p>Prescreen for psychiatric symptoms.</p> <p>Monitor carefully for CNS symptoms.</p> <p>Use with caution in the presence of drugs that increase RAL concentration.</p>	Consider drug substitution (RAL or coadministered drug) in cases of severe insomnia or other neuropsychiatric symptoms.

**Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	DTG	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• 7–30 days after starting DTG</li> </ul> <p><b>Presentation</b></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> <li>• Depression or exacerbation of preexisting depression</li> <li>• Anxiety</li> <li>• Suicidal ideation or attempted/completed suicide</li> <li>• <b>Drowsiness</b></li> <li>• <b>Neurocognitive deficits (lower total competence and school performance)</b></li> </ul> <p><i>Other CNS Manifestations (Generally Mild):</i></p> <ul style="list-style-type: none"> <li>• Sleep disturbances</li> <li>• Dizziness</li> <li>• Headache</li> </ul>	<p><b>Children:</b></p> <ul style="list-style-type: none"> <li>• <b>In a retrospective cohort analysis, neuropsychiatric events that resulted in discontinuation occurred in two of 29 (6.8%) children who initiated DTG.</b></li> </ul> <p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>• <b>2.7% of the neuropsychiatric AEs reported in a large prospective cohort resulted in treatment discontinuation.</b></li> <li>• Higher frequency of neuropsychiatric symptoms reported with DTG than with other INSTIs. A class effect has been suggested.</li> </ul>	<p>Pre-existing depression or other psychiatric illness</p> <p><b>History of ARV-related neuropsychiatric symptoms</b></p> <p>Higher frequency of neuropsychiatric symptoms reported when DTG is coadministered with ABC; however, evidence is conflicting.</p> <p>UGT1A1*6 and/or *28 polymorphism (reported in patients of Asian descent)</p>	<p>Use with caution in the presence of psychiatric illness, especially in patients with depression or a history of ARV-related neuropsychiatric symptoms.</p> <p>Consider morning dosing of DTG.</p>	<p>For persistent or severe neuropsychiatric symptoms, consider discontinuing DTG if a suitable alternative exists.</p> <p>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</p>

**Table 15a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	BIC	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>1–63 days after starting BIC (as late as 233 days for schizoaffective disorders)</li> </ul> <p><b>Presentation</b></p> <p><i>Neuropsychiatric Symptoms:</i></p> <ul style="list-style-type: none"> <li>Depression or exacerbation of pre-existing depression</li> <li>Suicidal ideation or attempted suicide</li> <li>Schizoaffective disorders</li> <li>Anxiety</li> </ul> <p><i>Other CNS Manifestations (Generally Mild):</i></p> <ul style="list-style-type: none"> <li>Abnormal dreams</li> <li>Dizziness</li> <li>Insomnia</li> </ul>	<p>Data in children and adults come mostly from clinical trials. Overall, the frequency of neuropsychiatric events in BIC and DTG comparator arms appeared similar in adult clinical trials.</p> <p><b>Children:</b></p> <ul style="list-style-type: none"> <li>1 child (1%) had Grade 2 insomnia and anxiety that led to drug discontinuation.</li> </ul> <p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>Abnormal dreams, dizziness, and insomnia occurred in 1% to 5% of adults.</li> <li>Suicidal ideation, suicide attempts, schizoaffective disorders, and depression occurred in &lt;1% of adults.</li> </ul>	<p>Pre-existing depression or other psychiatric conditions</p> <p>History of ARV-related neuropsychiatric symptoms</p>	<p>Use with caution in the presence of psychiatric conditions, or in patients with a history of ARV-related neuropsychiatric symptoms.</p>	<p>For persistent or severe neuropsychiatric symptoms, consider discontinuing BIC if a suitable alternative exists.</p> <p>For mild symptoms, continue BIC and counsel patient that symptoms will likely resolve with time.</p>

**Key:** ABC = abacavir; ARV = antiretroviral; BIC = bicitegravir; 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

## References

- Arenas-Pinto A, Grund B, Sharma S, et al. Increased risk of suicidal behaviour with use of efavirenz: results from the START trial. Presented at: 21st International AIDS Conference. 2016. Durban, South Africa.
- Bracchi M, Pagani N, et al. Multicentre open-label pilot study of switching from efavirenz to dolutegravir for central nervous system (CNS) toxicity. Abstract # P209. Presented at: HIV Drug Therapy. 2016. Glasgow, Scotland. Available at: <http://hivglasgow.org/2016-abstracts>.
- Briand C, Dollfus C, Faye A, et al. Efficacy and tolerance of dolutegravir-based combined ART in perinatally HIV-1-infected adolescents: a French multicentre retrospective study. *J Antimicrob Chemother*. 2017;72(3):837-843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27999017>.
- Cabrera Figueroa S, Fernandez de Gatta M, Hernandez Garcia L, et al. The convergence of therapeutic drug monitoring and pharmacogenetic testing to optimize efavirenz therapy. *Ther Drug Monit*. 2010;32(5):579-585. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20720517>.
- Cattaneo D, Ripamonti D, Baldelli S, Cozzi V, Conti F, Clementi E. Exposure-related effects of atazanavir on the pharmacokinetics of raltegravir in HIV-1-infected

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- patients. *Ther Drug Monit.* 2010;32(6):782-786. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20926993>.
6. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS.* 2013;27(6):939-950. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23211772>.
  7. de Boer MG, van den Berk GE, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. *AIDS.* 2016;30(18):2831-2834. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27824625>.
  8. Fernandez C, Michie K, et al. Adverse events and discontinuation of dolutegravir-based therapy in naive and experienced HIV patients: tertiary HIV centre experience. Abstract # P212. Presented at: HIV Drug Therapy. 2016. Glasgow, Scotland. Available at: <http://hivglasgow.org/2016-abstracts>.
  9. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. *J Acquir Immune Defic Syndr.* 2017;74(4):423-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27984559>.
  10. Rilpivirine [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/202022s011lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202022s011lbl.pdf).
  11. Food and Drug Administration. FDA drug safety communication: serious health problems seen in premature babies given kaletra (lopinavir/ritonavir) oral solution. 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm246002.htm>.
  12. Ford N, Shubber Z, Pozniak A, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: A systematic review and meta-analysis of randomized trials. *J Acquir Immune Defic Syndr.* 2015;69(4):422-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25850607>.
  13. García-Navarro C, Jiménez de Ory S, Navarro Gómez ML, et al. Sleep disturbances in a cohort of HIV-infected children and adolescents on antiretroviral treatment. Presented at: 22nd Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, WA.
  14. Group ES, Carey D, Puls R, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis.* 2015;15(7):793-802. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25877963>.
  15. Haas DW, Ribaud HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an adult AIDS clinical trials group study. *AIDS.* 2004;18(18):2391-2400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15622315>.
  16. Hauptfleisch MP, Moore DP, Rodda JL. Efavirenz as a cause of ataxia in children. *S Afr Med J.* 2015;105(11):897-898. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26632310>.
  17. Kheloufi F, Allemant J, Mokhtari S, Default A. Psychiatric disorders after starting dolutegravir: report of four cases. *AIDS.* 2015;29(13):1723-1725. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26372287>.
  18. Leutscher PD, Stecher C, Storgaard M, Larsen CS. Discontinuation of efavirenz therapy in HIV patients due to neuropsychiatric adverse effects. *Scand J Infect Dis.* 2013;45(8):645-651. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23427878>.
  19. Lombaard J, Bunupuradah T. Week 48 safety and efficacy of a rilpivirine (TMC278)-based regimen in HIV-infected treatment-naive adolescents: PAINT Phase II trial. Presented at: 7th International Workshop on HIV Pediatrics. 2015. Vancouver, Canada.
  20. Madeddu G, Menzaghi B, Ricci E, et al. Raltegravir central nervous system tolerability in clinical practice: results from a multicenter observational study. *AIDS.* 2012;26(18):2412-2415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23032413>.

21. Mills A, Garner W, Pozniak A, et al. Patient-reported symptoms over 48 weeks in a randomized, open-label, Phase IIIb non-inferiority trial of adults with HIV switching to co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir DF versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir DF. *Patient*. 2015;8(4):359-371. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26045359>.
22. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med*. 2014;161(1):1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24979445>.
23. Mollan KR, Tierney C, Eron JJ, et al. Composite CYP2B6/CYP2A6 genotype and risk for suicidality among HIV-infected individuals randomly assigned to initiate efavirenz-containing regimens in AIDS Clinical Trials Group studies. Presented at: 21st International AIDS Conference. 2016. Durban, South Africa.
24. Nachman S, et al. IMPAACT P1066: raltegravir (RAL) safety and efficacy in HIV infected (+) youth two to 18 years of age through week 48. Abstract no. TUAB0205. Presented at: 19th International AIDS Conference. 2012. Washington, DC.
25. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. *J Int AIDS Soc*. 2014;17:19214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25192857>.
26. Nkhoma ET, Coumbis J, Farr AM, et al. No evidence of an association between efavirenz exposure and suicidality among HIV patients initiating antiretroviral therapy in a retrospective cohort study of real world data. *Medicine*. 2016;95(3):e2480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26817882>.
27. Pinillos F, Dandara C, Swart M, et al. Case report: severe central nervous system manifestations associated with aberrant efavirenz metabolism in children: the role of CYP2B6 genetic variation. *BMC Infect Dis*. 2016;16:56. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26831894>.
28. Puthanakit T, Tanpaiboon P, Aурpibul L, Cressey TR, Sirisanthana V. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther*. 2009;14(3):315-320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19474465>.
29. Quercia R, Roberts J. Psychiatric adverse events from the DTG ART-naive Phase 3 clinical trials. Abstract # P210. Presented at: HIV Drug Therapy. 2016. Glasgow, Scotland. Available at: <http://hivglasgow.org/2016-abstracts>.
30. Rakhmanina NY, van den Anker JN, Soldin SJ, van Schaik RH, Mordwinkin N, Neely MN. Can therapeutic drug monitoring improve pharmacotherapy of HIV infection in adolescents? *Ther Drug Monit*. 2010;32(3):273-281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20445485>.
31. Reiss KA, Bailey JR, Pham PA, Gallant JE. Raltegravir-induced cerebellar ataxia. *AIDS*. 2010;24(17):2757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20980871>.
32. Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS*. 2013;27(9):1403-1412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23343913>.
33. Smith C, Ryom L, Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25394021>.
34. Strehlau R, Martens L, Coovadia A, et al. Absence seizures associated with efavirenz initiation. *Pediatr Infect Dis J*. 2011;30(11):1001-1003. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21633320>.
35. Tepler H, Brown DD, Leavitt RY, et al. Long-term safety from the raltegravir clinical development program. *Current HIV Res*. 2011;9(1):40-53. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21198432>.
36. Todd S, Rafferty P, Walker E, et al. Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. *Int J STD AIDS*. 2017;956462416688127.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28118801>.

37. van Dijk JH, Sutcliffe CG, Hamangaba F, Bositis C, Watson DC, Moss WJ. Effectiveness of efavirenz-based regimens in young HIV-infected children treated for tuberculosis: a treatment option for resource-limited settings. *PLoS One*. 2013;8(1):e55111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23372824>.
38. Variava E, Sigauke FR, Norman J, et al. Brief report: late efavirenz-induced ataxia and encephalopathy: a case series. *J Acquir Immune Defic Syndr*. 2017;75(5):577-579. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28520619>.
39. Viswanathan P, Baro E, Soon G, Sherwat A, Struble KA. Neuropsychiatric adverse events associated with integrase strand transfer inhibitors. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
40. Walmsley S, Baumgarten A, Berenguer J, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26262777>.
41. Waters L, Fisher M, Winston A, et al. A Phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS*. 2011;25(1):65-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21099666>.
42. Arenas-Pinto A, Grund B, Sharma S, et al. Risk of suicidal behavior with use of efavirenz: results from the strategic timing of antiretroviral treatment trial. *Clin Infect Dis*. 2018;67(3):420-429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29538636>.
43. Capetti AF, Di Giambenedetto S, Latini A, et al. Morning dosing for dolutegravir-related insomnia and sleep disorders. *HIV Med*. 2018;19(5):e62-e63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28762661>.
44. Van de Wijer L, McHaile DN, de Mast Q, et al. Neuropsychiatric symptoms in Tanzanian HIV-infected children receiving long-term efavirenz treatment: a multicentre, cross-sectional, observational study. *Lancet HIV*. 2019;6(4):e250-e258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30770324>.
45. Hammond CK, Eley B, Ing N, Wilmshurst JM. Neuropsychiatric and neurocognitive manifestations in HIV-infected children treated with efavirenz in South Africa—a retrospective case series. *Front Neurol*. 2019;10:742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31338063>.
46. Burman RJ, Wilmshurst JM, Gebauer S, Weise L, Walker KG, Donald KA. Seizures in children with HIV infection in South Africa: a retrospective case control study. *Seizure*. 2019;65:159-165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30721872>.
47. Cuzin L, Pugliese P, Katlama C, et al. Integrase strand transfer inhibitors and neuropsychiatric adverse events in a large prospective cohort. *J Antimicrob Chemother*. 2019;74(3):754-760. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30534993>.
48. Hoffmann C, Llibre JM. Neuropsychiatric Adverse events with dolutegravir and other integrase strand transfer inhibitors. *AIDS Rev*. 2019;21(1):4-10. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30899113>.

**Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Dyslipidemia</b>	<p><b>PIs:</b></p> <ul style="list-style-type: none"> <li>All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV, with or without RTV.</li> </ul> <p><b>NRTIs:</b></p> <ul style="list-style-type: none"> <li>Lower incidence reported with TDF than with TAF.</li> </ul> <p><b>NNRTIs:</b></p> <ul style="list-style-type: none"> <li>Lower incidence reported with NVP, RPV, and ETR than with EFV.</li> </ul>	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>As early as 2 weeks to months after beginning therapy</li> </ul> <p><b>Presentation</b></p> <p><i>PIs:</i></p> <ul style="list-style-type: none"> <li>↑ LDL-C, TC, and TG</li> </ul> <p><i>NRTIs:</i></p> <ul style="list-style-type: none"> <li>↑ LDL-C, TC, and TG</li> </ul> <p><i>NNRTIs:</i></p> <ul style="list-style-type: none"> <li>↑ LDL-C, TC, and HDL-C</li> </ul>	<p>Reported frequency varies with specific ARV regimen, duration of ART, and the specific laboratory parameters used to diagnose lipid abnormalities.</p> <p>10% to 20% of young children receiving LPV/r will have lipid abnormalities.</p> <p>40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities.</p> <p>Higher abnormal fasting serum lipids have been observed in ART-naïve adults who received EVG/c/FTC/TAF than in those who received EVG/c/FTC/TDF.</p> <p>Increase in serum lipids from baseline has also been noted in adolescents receiving EVG/c/FTC/TAF.</p>	<p>Advanced-stage HIV disease</p> <p>High-fat, high-cholesterol diet</p> <p>Lack of exercise</p> <p>Obesity</p> <p>Hypertension</p> <p>Smoking</p> <p>Family history of dyslipidemia or premature ASCVD</p> <p>Metabolic syndrome</p> <p>Fat maldistribution</p>	<p><b>Prevention:</b></p> <ul style="list-style-type: none"> <li>Low-fat diet</li> <li>Exercise</li> <li>Smoking-prevention counseling</li> <li>When possible, use ARVs associated with a lower prevalence of dyslipidemia. These include INSTIs and newer PIs (e.g., ATV, DRV).</li> </ul> <p><b>Monitoring<sup>a</sup></b></p> <p><i>Adolescents and Adults:</i></p> <ul style="list-style-type: none"> <li>Obtain FLP (TC, HDL-C, non-HDL-C, LDL-C, and TG) twice (&gt;2 weeks but ≤3 months apart, average these results) Monitor FLP every 6 months (for abnormal results) or every 12 months (for normal results).</li> </ul> <p><i>Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:</i></p> <ul style="list-style-type: none"> <li>Obtain nonfasting screening lipid profiles at entry into care and then every 6–12 months, depending on the results.</li> <li>If TG or LDL-C is elevated or if a patient has additional risk factors, obtain FLP.</li> </ul> <p><i>Children with Lipid Abnormalities and/or Additional Risk Factors:</i></p> <ul style="list-style-type: none"> <li>Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated).</li> </ul> <p><i>Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:</i></p> <ul style="list-style-type: none"> <li>Obtain 12-hour FLP, LFT, and CK at 4 weeks, 8 weeks, and 3 months after starting lipid therapy.</li> </ul>	<p>Assess all patients for additional ASCVD risk factors. Patients with HIV are considered to be at moderate risk of ASCVD.<sup>b</sup></p> <p>ARV regimen changes should be considered, especially when the patient is receiving older PIs (e.g., LPV/r) and/or RTV boosting. Switching to a PI-sparing regimen, a PI-based regimen with a more favorable lipid profile, or COBI boosting causes a decline in LDL-C or TG values. However, the lipid-lowering effect for LDL-C is less pronounced than with statin therapy.</p> <p>Refer patients to a lipid specialist early if LDL-C is ≥250 mg/dL or TG is ≥500 mg/dL.</p> <p>If LDL-C is ≥130 mg/dL but &lt;250 mg, or TG is ≥150 mg/dL but &lt;500 mg/dL, the following staged treatment approach is recommended by the NHLBI guidelines:<sup>b</sup></p> <ul style="list-style-type: none"> <li>Implement diet, nutrition, and lifestyle management for 6–9 months. Consult with a dietician if one is available.</li> <li>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.</li> <li>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.<sup>b</sup></li> </ul>

**Table 15b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia, continued					<ul style="list-style-type: none"> <li>If there are minimal alterations in AST, ALT, and CK, monitor every 3–4 months during the first year and every 6 months thereafter (or as clinically indicated).</li> <li>Repeat FLP 4 weeks after increasing doses of antihyperlipidemic agents.</li> </ul>	<ul style="list-style-type: none"> <li>Drug therapy can be considered in cases of severe hypertriglyceridemia (TG <math>\geq</math>500 mg/dL). Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used.</li> </ul> <p>The long-term risks of lipid abnormalities in children who are receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature ASCVD.</p>

<sup>a</sup> Given the burden of collecting fasting blood samples, some practitioners routinely measure cholesterol and TG from nonfasting blood samples and follow up abnormal values with a test done in the fasted state.

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

**Key:** ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; DRV = darunavir; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; 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 = triglycerides

## References

- Tassiopoulos K, Williams PL, Seage GR, 3rd, et al. Association of hypercholesterolemia incidence with antiretroviral treatment, including protease inhibitors, among perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2008;47(5):607-614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18209684>.
- Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-672. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19279441>.
- Rhoads MP, Lanigan J, Smith CJ, Lyall EG. Effect of specific ART drugs on lipid changes and the need for lipid management in children with HIV. *J Acquir Immune Defic Syndr*. 2011;57(5):404-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21499114>.
- Jacobson DL, Williams P, Tassiopoulos K, Melvin A, Hazra R, Farley J. Clinical management and follow-up of hypercholesterolemia among perinatally HIV-infected children enrolled in the PACTG 219C study. *J Acquir Immune Defic Syndr*. 2011;57(5):413-420. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21602698>.
- O'Gorman CS, O'Neill MB, Conwell LS. Considering statins for cholesterol-reduction in children if lifestyle and diet changes do not improve their health: a review of the risks and benefits. *Vasc Health Risk Manag*. 2011;7:1-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21339908>.

6. Singh S, Willig JH, Mugavero MJ, et al. Comparative effectiveness and toxicity of statins among HIV-infected patients. *Clin Infect Dis*. 2011;52(3):387-395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21189273>.
7. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Integrated guidelines for cardiovascular health and risk reduction in children and adolescents. 2012. Available at: [https://www.nhlbi.nih.gov/files/docs/peds\\_guidelines\\_sum.pdf](https://www.nhlbi.nih.gov/files/docs/peds_guidelines_sum.pdf).
8. Food and Drug Administration. FDA drug safety communication: interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk of muscle injury. 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm293877.htm>.
9. Langat A, Benki-Nugent S, Wamalwa D, et al. Lipid changes in Kenyan HIV-1-infected infants initiating highly active antiretroviral therapy by 1 year of age. *Pediatr Infect Dis J*. 2013;32(7):e298-304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23385950>.
10. Casado JL, de Los Santos I, Del Palacio M, et al. Lipid-lowering effect and efficacy after switching to etravirine in HIV-infected patients with intolerance to suppressive HAART. *HIV Clin Trials*. 2013;14(1):1-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23372109>.
11. Lazzaretti RK, Kuhmmer R, Sprinz E, Polanczyk CA, Ribeiro JP. Dietary intervention prevents dyslipidemia associated with highly active antiretroviral therapy in human immunodeficiency virus type 1-infected individuals: a randomized trial. *J Am Coll Cardiol*. 2012;59(11):979-988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22402068>.
12. Strehlau R, Coovadia A, Abrams EJ, et al. Lipid profiles in young HIV-infected children initiating and changing antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012;60(4):369-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22134152>.
13. Hazra R, Cohen RA, Gonin R, et al. Lipid levels in the second year of life among HIV-infected and HIV-exposed uninfected Latin American children. *AIDS*. 2012;26(2):235-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22008654>.
14. Arpadi S, Shiao S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child*. 2013;98(4):258-264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23220209>.
15. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc*. 2013;16:18600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782481>.
16. Blazquez D, Ramos-Amador JT, Sainz T, et al. Lipid and glucose alterations in perinatally-acquired HIV-infected adolescents and young adults. *BMC Infect Dis*. 2015;15:119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25880777>.
17. Bwakura-Dangarembizi M, Musiime V, Szubert AJ, et al. Prevalence of lipodystrophy and metabolic abnormalities in HIV-infected African children after 3 years on first-line antiretroviral therapy. *Pediatr Infect Dis J*. 2015;34(2):e23-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25068287>.
18. Dejkhamron P, Unachak K, Aurpibul L, Sirisanthana V. Insulin resistance and lipid profiles in HIV-infected Thai children receiving lopinavir/ritonavir-based highly active antiretroviral therapy. *J Pediatr Endocrinol Metab*. 2014;27(5-6):403-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24259240>.
19. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on antiretroviral therapy. *Pediatr Infect Dis J*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26421804>.
20. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25890673>.

21. Lee FJ, Monteiro P, Baker D, et al. Rosuvastatin vs. protease inhibitor switching for hypercholesterolaemia: a randomized trial. *HIV Med.* 2016;17(8):605-614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26987376>.
22. Ramteke SM, Shiau S, Foca M, et al. Patterns of growth, body composition, and lipid profiles in a South African cohort of human immunodeficiency virus-infected and uninfected children: a cross-sectional study. *J Pediatric Infect Dis Soc.* 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28481997>.
23. Melvin AJ, Montepiedra G, Aaron L, et al. Safety and efficacy of atorvastatin in human immunodeficiency virus-infected children, adolescents and young adults with hyperlipidemia. *Pediatr Infect Dis J.* 2017;36(1):53-60. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27749649>.
24. Jao J, Yu W, Patel K, et al. Improvement in lipids after switch to boosted atazanavir or darunavir in children/adolescents with perinatally acquired HIV on older protease inhibitors: results from the Pediatric HIV/AIDS Cohort Study. *HIV Med.* 2018;19(3):175-183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29159965>.
25. Echecopar-Sabogal J, D'Angelo-Piaggio L, Chaname-Baca DM, Ugarte-Gil C. Association between the use of protease inhibitors in highly active antiretroviral therapy and incidence of diabetes mellitus and/or metabolic syndrome in HIV-infected patients: A systematic review and meta-analysis. *Int J STD AIDS.* 2018;29(5):443-452. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28956700>.
26. Echeverria P, Bonjoch A, Puig J, Ornella A, Clotet B, Negredo E. Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia. *HIV Med.* 2017;18(10):782-786. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28671337>.
27. Vieira ADS, Silveira G. Effectiveness of n-3 fatty acids in the treatment of hypertriglyceridemia in HIV/AIDS patients: a meta-analysis. *Cien Saude Colet.* 2017;22(8):2659-2669. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28793080>.
28. Cid-Silva P, Fernandez-Bargiela N, Margusino-Framinan L, et al. Treatment with tenofovir alafenamide fumarate worsens the lipid profile of HIV-infected patients versus treatment with tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine. *Basic Clin Pharmacol Toxicol.* 2019;124(4):479-490. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30388308>.
29. Patel K, Lindsey J, Angelidou K, Aldrovandi G, Palumbo P, Team IPS. Metabolic effects of initiating lopinavir/ritonavir-based regimens among young children. *AIDS.* 2018;32(16):2327-2336. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30102656>.
30. Taramasso L, Tatarelli P, Ricci E, et al. Improvement of lipid profile after switching from efavirenz or ritonavir-boosted protease inhibitors to rilpivirine or once-daily integrase inhibitors: results from a large observational cohort study (SCOLTA). *BMC Infect Dis.* 2018;18(1):357. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30064371>.
31. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation.* 2019;139(25):e1046-e1081. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30565953>.

**Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects** (Last updated April 16, 2019; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Nausea/Vomiting</b>	All ARV drugs, but most notably RTV-boosted PIs	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Early</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Nausea and emesis, both of which may be associated with anorexia and/or abdominal pain</li> </ul>	Varies by ARV agent; generally <15%	Unknown	<p>Instruct patient to take PIs with food.</p> <p>Monitor for weight loss and ARV adherence.</p>	<p>Reassure patient that these adverse effects generally improve over time (usually in 6–8 weeks).</p> <p>Consider switching to ARV drugs with smaller tablet sizes (see <a href="#">Appendix A, Table 2</a>).</p> <p>Provide supportive care.</p> <p>In extreme or persistent cases, use antiemetics or switch to another ARV regimen.</p>
<b>Diarrhea</b>	All ARV drugs, but most notably RTV-boosted PIs	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Early</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• More frequent bowel movements and stools that are generally soft</li> </ul>	Varies by ARV agent; generally <15%	Unknown	Monitor for weight loss and dehydration.	<p>In prolonged or severe cases, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea.</p> <p>Reassure patient that this adverse effect generally improves over time (usually in 6–8 weeks). Consider switching to another ARV regimen in persistent and severe cases.</p> <p>Treatment data in children are lacking; however, the following strategies may be useful when the ARV regimen cannot be changed:</p> <ul style="list-style-type: none"> <li>• Dietary modification</li> <li>• Using bulk-forming agents (e.g., psyllium)</li> <li>• Using antimotility agents (e.g., loperamide)</li> <li>• Using crofelemer, which is approved by the FDA to treat ART-associated diarrhea in adults aged ≥18 years; no pediatric data are available.</li> </ul>

**Table 15c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects** (Last updated April 16, 2019; **last reviewed April 14, 2020**) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Pancreatitis</b>	Rare, but may occur with NRTIs or RTV-boosted PIs	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Any time, usually after months of therapy</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Emesis, abdominal pain, elevated amylase and lipase levels (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)</li> </ul>	<2% in a recent case series	<p>Use of concomitant medications that are associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin)</p> <p>Hypertriglyceridemia</p> <p>Advanced HIV infection</p> <p>Previous episode of pancreatitis</p> <p>Alcohol use</p>	Measure serum amylase and lipase concentrations if persistent abdominal pain develops.	<p>Discontinue offending agent and <b>avoid reintroduction.</b></p> <p>Manage symptoms of acute episodes.</p> <p>If pancreatitis is associated with hypertriglyceridemia, consider using interventions to lower TG levels.</p>

**Key:** 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

## References

- Buck WC, Kabue MM, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children. *J Int AIDS Soc.* 2010;13:31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20691049>.
- Nachman SA, Chernoff M, Gona P, et al. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med.* 2009;163(2):164-171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19188649>.
- Hoffmann CJ, Fielding KL, Charalambous S, et al. Antiretroviral therapy using zidovudine, lamivudine, and efavirenz in South Africa: tolerability and clinical events. *AIDS.* 2008;22(1):67-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18090393>.
- Malan N, Su J, Mancini M, et al. Gastrointestinal tolerability and quality of life in antiretroviral-naive HIV-1-infected patients: data from the CASTLE study. *AIDS Care.* 2010;22(6):677-686. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20467943>.
- Manfredi R, Calza L. HIV infection and the pancreas: risk factors and potential management guidelines. *Int J STD AIDS.* 2008;19(2):99-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18334062>.
- Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr.* 2012;59(3):274-280. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22126740>.
- Wegzyn CM, Fredrick LM, Stubbs RO, Woodward WC, Norton M. Diarrhea associated with lopinavir/ritonavir-based therapy: results of a meta-analysis of 1469

- HIV-1-infected participants. *J Int Assoc Physicians AIDS Care (Chic)*. 2012;11(4):252-259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22544446>.
8. Oumar AA, Diallo K, Dembele JP, et al. Adverse drug reactions to antiretroviral therapy: prospective study in children in sikasso (mali). *J Pediatr Pharmacol Ther*. 2012;17(4):382-388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23411444>.
  9. Wattanuchariya N, Sirisanthana V, Oberdorfer P. Effectiveness and safety of protease inhibitor-based regimens in HIV-infected Thai children failing first-line treatment. *HIV Med*. 2013;14(4):226-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23094820>.
  10. Van Dyke RB, Wang L, Williams PL, Pediatric AIDS Clinical Trials Group C Team. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. 2008;198(11):1599-1608. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19000014>.
  11. Clay PG, Crutchley RD. Noninfectious diarrhea in HIV seropositive individuals: a review of prevalence rates, etiology, and management in the era of combination antiretroviral therapy. *Infect Dis Ther*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25388760>.
  12. Szoke D, Ridolfo A, Valente C, Galli M, Panteghini M. Frequency of pancreatic hyperamylasemia in human immunodeficiency virus-positive patients in the highly active antiretroviral therapy era. *Am J Clin Pathol*. 2016;145(1):128-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26712880>.
  13. Castro JG, Chin-Beckford N. Crofelemer for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy. *Expert Rev Clin Pharmacol*. 2015;8(6):683-690. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26517110>.
  14. Dikman AE, Schonfeld E, Srisarajivakul NC, Poles MA. Human Immunodeficiency virus-associated diarrhea: still an issue in the era of antiretroviral therapy. *Dig Dis Sci*. 2015;60(8):2236-2245. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25772777>.
  15. Logan C, Beadsworth MB, Beeching NJ. HIV and diarrhoea: what is new? *Curr Opin Infect Dis*. 2016;29(5):486-494. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27472290>.

**Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Anemia<sup>a</sup></b>	ZDV	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Variable; weeks to months after starting therapy</li> </ul> <p><b>Presentation</b></p> <p><i>More Common:</i></p> <ul style="list-style-type: none"> <li>Asymptomatic</li> <li>Mild fatigue</li> <li>Pallor</li> <li>Tachypnea</li> </ul> <p><i>Rare:</i></p> <ul style="list-style-type: none"> <li>Congestive heart failure</li> </ul>	<p><b>Newborns Exposed to HIV:</b></p> <ul style="list-style-type: none"> <li>Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir.</li> </ul> <p><b>Children with HIV Who Are Taking ARV Drugs:</b></p> <ul style="list-style-type: none"> <li>Anemia is two to three times more common with ZDV-containing regimens than with all other regimens.</li> </ul>	<p><b>Newborns Exposed to HIV:</b></p> <ul style="list-style-type: none"> <li>Premature birth <b>is the most common risk factor</b></li> <li><i>In utero</i> exposure to ZDV-containing regimens</li> <li>Advanced maternal HIV</li> <li>Neonatal blood loss</li> <li>Combination ARV prophylaxis or <b>presumptive</b> HIV therapy, particularly ZDV plus 3TC</li> </ul> <p><b>Children with HIV Who Are Taking ARV Drugs:</b></p> <ul style="list-style-type: none"> <li>Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency)</li> <li>Myelosuppressive drugs (e.g., TMP-SMX, rifabutin)</li> <li>Iron deficiency</li> <li>Advanced or poorly controlled HIV disease</li> <li>OIs of the bone marrow</li> <li>Malnutrition</li> </ul>	<p><b>Newborns Exposed to HIV:</b></p> <ul style="list-style-type: none"> <li>Obtain CBC at birth.</li> <li>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.</li> </ul> <p><b>Children with HIV Who Are Taking ARV Drugs:</b></p> <ul style="list-style-type: none"> <li>Avoid using ZDV in children with severe anemia when alternative agents are available.</li> <li>Obtain CBC as part of routine care (see <a href="#">Clinical and Laboratory Monitoring of Pediatric HIV Infection</a>).</li> </ul>	<p><b>Newborns Exposed to HIV:</b></p> <ul style="list-style-type: none"> <li>Anemia rarely requires intervention unless it is symptomatic or Hgb &lt;7.0 g/dL.</li> <li>ZDV administration can be limited to 4 weeks in low-risk neonates (see <a href="#">Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection</a>).</li> </ul> <p><b>Children with HIV Who Are Taking ARV Drugs:</b></p> <ul style="list-style-type: none"> <li>Discontinue non-ARV, marrow-toxic drugs, if feasible.</li> <li>Treat coexisting iron deficiency, OIs, and malignancies.</li> <li>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.</li> </ul>
<b>Macrocytosis</b>	ZDV	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Within days or weeks of starting therapy</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Asymptomatic, but MCV is often &gt;100 fL</li> <li>Sometimes associated with anemia</li> </ul>	>90% to 95% for all ages	None	No monitoring required—macrocytosis can be detected if CBC is obtained as part of routine care (see <a href="#">Clinical and Laboratory Monitoring of Pediatric HIV Infection</a> ).	No management required.

**Table 15d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neutropenia <sup>a</sup>	ZDV	<b>Onset:</b> <ul style="list-style-type: none"> <li>• Variable</li> </ul> <b>Presentation:</b> <ul style="list-style-type: none"> <li>• Asymptomatic</li> </ul>	<b>Newborns Exposed to HIV:</b> <ul style="list-style-type: none"> <li>• Rare</li> </ul> <b>Children with HIV Who Are Taking ARV Drugs:</b> <ul style="list-style-type: none"> <li>• 2% to 4% of children on ARV drugs</li> <li>• Highest rates occur in children on ZDV-containing regimens</li> </ul>	<b>Newborns Exposed to HIV:</b> <ul style="list-style-type: none"> <li>• <i>In utero</i> exposure to ARV drugs</li> <li>• Combination ARV prophylaxis, particularly ZDV plus 3TC</li> </ul> <b>Children with HIV Who Are Taking ARV Drugs:</b> <ul style="list-style-type: none"> <li>• Advanced or poorly controlled HIV infection</li> <li>• Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin)</li> </ul>	<b>Children with HIV Who Are Taking ARV Drugs:</b> <ul style="list-style-type: none"> <li>• Obtain CBC as part of routine care.</li> </ul>	<b>Newborns Exposed to HIV:</b> <ul style="list-style-type: none"> <li>• No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC reaches &lt;500 cells/mm<sup>3</sup>. ZDV administration can be limited to 4 weeks in low-risk neonates (see <a href="#">Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection</a>).</li> </ul> <b>Children with HIV Who Are Taking ARV Drugs:</b> <ul style="list-style-type: none"> <li>• Discontinue non-ARV, marrow-toxic drugs, if feasible.</li> <li>• Treat coexisting OIs and malignancies.</li> <li>• In cases of persistent, severe neutropenia that is thought to be associated with ARV drugs, switch to a regimen that does not contain ZDV.</li> </ul>

<sup>a</sup> HIV infection itself, OIs, and medications that are used to prevent OIs (e.g., TMP-SMX) may all contribute to anemia and neutropenia.

**Key:** 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

## References

1. Lahoz R, Noguera A, Rovira N, et al. Antiretroviral-related hematologic short-term toxicity in healthy infants: implications of the new neonatal 4-week zidovudine regimen. *Pediatr Infect Dis J*. 2010;29(4):376-379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19949355>.
2. Dryden-Peterson S, Shapiro RL, Hughes MD, et al. Increased risk of severe infant anemia after exposure to maternal HAART, Botswana. *J Acquir Immune Defic Syndr*. 2011;56(5):428-436. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21266910>.
3. Mocroft A, Lifson AR, Touloumi G, et al. Haemoglobin and anaemia in the SMART study. *Antivir Ther*. 2011;16(3):329-337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21555815>.
4. Nyesigire Ruhinda E, Bajunirwe F, Kiwanuka J. Anaemia in HIV-infected children: severity, types and effect on response to HAART. *BMC Pediatr*. 2012;12:170. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23114115>.

5. Esan MO, Jonker FA, Hensbroek MB, Calis JC, Phiri KS. Iron deficiency in children with HIV-associated anaemia: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg*. 2012;106(10):579-587. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22846115>.
6. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716975>.
7. Renner LA, Dicko F, Koueta F, et al. Anaemia and zidovudine-containing antiretroviral therapy in paediatric antiretroviral programmes in the IeDEA Paediatric West African Database to evaluate AIDS. *J Int AIDS Soc*. 2013;16(1):18024. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24047928>.
8. Arrow Trial team, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet*. 2013;381(9875):1391-1403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23473847>.
9. Bunupuradah T, Kariminia A, Chan KC, et al. Incidence and predictors of severe anemia in Asian HIV-infected children using first-line antiretroviral therapy. *Int J Infect Dis*. 2013;17(10):e806-810. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23764352>.
10. Van Dyke RB, Wang L, Williams PL, Pediatric ACTGCT. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. 2008;198(11):1599-1608. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19000014>.
11. Smith C, Forster JE, Levin MJ, et al. Serious adverse events are uncommon with combination neonatal antiretroviral prophylaxis: a retrospective case review. *PLoS One*. 2015;10(5):e0127062. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26000984>.
12. Smith C, Weinberg A, Forster JE, et al. Maternal lopinavir/ritonavir is associated with fewer adverse events in infants than nelfinavir or atazanavir. *Infect Dis Obstet Gynecol*. 2016;2016:9848041. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27127401>.
13. Shet A, Bhavani PK, Kumarasamy N, et al. Anemia, diet and therapeutic iron among children living with HIV: a prospective cohort study. *BMC Pediatr*. 2015;15:164. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26482352>.
14. Kibaru EG, Nduati R, Wamalwa D, Kariuki N. Impact of highly active antiretroviral therapy on hematological indices among HIV-1 infected children at Kenyatta National Hospital-Kenya: retrospective study. *AIDS Res Ther*. 2015;12:26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26279668>.
15. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis*. 2016;16(2):169-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26481928>.
16. Lau E, Brophy J, Samson L, et al. Nevirapine pharmacokinetics and safety in neonates receiving combination antiretroviral therapy for prevention of vertical HIV transmission. *J Acquir Immune Defic Syndr*. 2017;74(5):493-498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28114187>.
17. The European Pregnancy and Paediatric HIV Cohort Collaboration Study Group in EuroCoord. Safety of zidovudine/lamivudine scored tablets in children with HIV infection in Europe and Thailand. *Eur J of Clin Pharmacol*. 2017;73(4):463-468. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5350228/>.
18. Melvin AJ, Warshaw M, Compagnucci A, et al. Hepatic, renal, hematologic, and inflammatory markers in HIV-infected children on long-term suppressive antiretroviral therapy. *J Pediatric Infect Dis Soc*. 2017;6(3):e109-e115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/3979993>.
19. European Pregnancy and Pediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord. Severe haematologic toxicity is rare in high risk HIV-exposed infants receiving combinatio neonatal prophylaxis. *HIV Med*. 2019;20(5):291-307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30844150>.

**Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events**  
 (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Hepatitis</b>	<p>Most ARV drugs have been associated with hepatitis, but there is a strong association between hepatitis and the use of NVP and EFV.</p> <p>NVP, EFV, ABC, RAL, DTG, and MVC have been associated with hepatitis in the context of HSRs.</p> <p>NRTIs, especially ZDV, have been associated with lactic acidosis and hepatic steatosis.</p>	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Acute toxic hepatitis most commonly occurs within the first few months of therapy, but it can occur later.</li> <li>Steatosis presents after months or years of therapy.</li> <li>Patients with HBV coinfection may experience a hepatitis flare 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 TDF and TAF have high barriers to resistance when used to treat HBV.</li> <li>Hepatitis may be a manifestation of IRIS if it occurs early in therapy, especially in patients with HBV or HCV coinfection.</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Asymptomatic elevation of AST and ALT levels</li> <li>Symptomatic hepatitis with nausea, fatigue, and jaundice</li> <li>Hepatitis may present in the context of HSR with rash, lactic acidosis, and hepatic steatosis.</li> </ul>	Uncommon	<p>HBV or HCV coinfection</p> <p>Underlying liver disease</p> <p>Use of other hepatotoxic medications and supplements (e.g., St. John's wort [<i>Hypericum perforatum</i>], chaparral [<i>Larrea tridentata</i>], germander [<i>Teucrium chamaedrys</i>])</p> <p>Alcohol use</p> <p>Pregnancy</p> <p>Obesity</p> <p>Higher drug concentrations of PIs</p> <p><b>For NVP-Associated Hepatic Events in Adults:</b></p> <ul style="list-style-type: none"> <li>Female sex with pre-NVP CD4 count &gt;250 cells/mm<sup>3</sup></li> <li>Male sex with pre-NVP CD4 count &gt;400 cells/mm<sup>3</sup></li> <li>Population-specific HLA types<sup>a</sup></li> </ul>	<p><b>Prevention:</b></p> <ul style="list-style-type: none"> <li>Avoid concomitant use of hepatotoxic medications.</li> <li>In patients with elevated levels of hepatic enzymes (&gt;5 times to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP.</li> </ul> <p><b>Monitoring</b></p> <p><i>For ARV Drugs Other Than NVP:</i></p> <ul style="list-style-type: none"> <li>Obtain AST and ALT levels at baseline and at least every 3–4 months thereafter;<sup>b</sup> monitor at-risk patients more frequently (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT levels).</li> </ul> <p><i>For NVP:</i></p> <ul style="list-style-type: none"> <li>Obtain AST and ALT levels at baseline, at 2 weeks, 4 weeks, and then every 3 months.</li> </ul>	<p>Evaluate the patient for other infectious and non-infectious causes of hepatitis and monitor the patient closely.</p> <p><b>Asymptomatic Hepatitis:</b></p> <ul style="list-style-type: none"> <li>Potentially offending ARV drugs should be discontinued if ALT or AST level is &gt;5 times ULN.</li> </ul> <p><b>Symptomatic Hepatitis:</b></p> <ul style="list-style-type: none"> <li>Discontinue all ARV drugs and other potentially hepatotoxic drugs.</li> <li>If a patient experiences hepatitis that is attributed to NVP, NVP <b>should be permanently discontinued</b>.</li> <li>Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV.</li> </ul>

**Table 15e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events**  
 (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Indirect Hyperbilirubinemia</b>	ATV	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Within the first months of therapy</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• May be asymptomatic or associated with jaundice</li> <li>• Levels of direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.</li> <li>• Normal AST and ALT</li> </ul>	In long-term follow-up, 9% of children who were receiving ATV had at least one total bilirubin level >5 times ULN and 1.4% of children experienced jaundice.	None established.	<p><b>Monitoring:</b></p> <ul style="list-style-type: none"> <li>• No ongoing monitoring needed.</li> <li>• After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.</li> </ul>	<p>Isolated indirect hyperbilirubinemia is not an indication to stop ATV.</p> <p>Psychological impact of jaundice should be evaluated, and alternative agents should be considered.</p> <p>Jaundice may result in nonadherence, particularly in adolescents; this side effect should be discussed with patients.</p>
<b>Non-Cirrhotic Portal Hypertension</b>	d4T, ddl The Panel <b>no longer recommends</b> the use of these agents.	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Generally after years of therapy; may occur years after stopping therapy.</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• GI bleeding, esophageal varices, and hypersplenism</li> <li>• Mild elevations in AST and ALT levels, moderate increases in ALP levels, and pancytopenia</li> </ul> <p><b>Liver Biopsy Findings:</b></p> <ul style="list-style-type: none"> <li>• The most commonly seen findings include nodular regenerative hyperplasia and hepatportal sclerosis.</li> </ul>	Rare	Prolonged exposure to ddl and the combination of d4T and ddl.	No specific monitoring	Manage complications of GI bleeding and esophageal varices.

<sup>a</sup> For example, HLA-DRB1\*0101 in white people, HLA-DRB1\*0102 in South Africans, and HLA-B35 in Thai people and white people.

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

**Key:** 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; d4T = stavudine; ddl = 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; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; RAL = raltegravir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ULN = upper limit of normal; ZDV = zidovudine

## References

### General Reviews

1. Aурipibul L, Bunupuradah T, Sophan S, et al. Prevalence and incidence of liver dysfunction and assessment of biomarkers of liver disease in HIV-infected Asian children. *Pediatr Infect Dis J*. 2015;34(6):e153-158. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25970117>.
2. Huntington S, Thorne C, Newell ML, et al. Pregnancy is associated with elevation of liver enzymes in HIV-positive women on antiretroviral therapy. *AIDS*. 2015;29(7):801-809. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25710412>.
3. Kovari H, Sabin CA, Ledergerber B, et al. Antiretroviral drugs and risk of chronic alanine aminotransferase elevation in human immunodeficiency virus (HIV)-monoinfected persons: the data collection on adverse events of anti-HIV drugs study. *Open Forum Infect Dis*. 2016;3(1):ofw009. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26925429>.
4. Navarro VJ, Khan I, Bjornsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65(1):363-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27677775>.
5. Sonderup MW, Wainwright HC. Human immunodeficiency virus infection, antiretroviral therapy, and liver pathology. *Gastroenterol Clin North Am*. 2017;46(2):327-343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28506368>.
6. The National Institute of Diabetes and Digestive and Kidney Diseases. Clinical and research information on drug-induced liver Injury. 2019. Available at: <https://livertox.nlm.nih.gov>.
7. Anadol E, Lust K, Boesecke C, et al. Exposure to previous cART is associated with significant liver fibrosis and cirrhosis in human immunodeficiency virus-infected patients. *PLoS One*. 2018;13(1):e0191118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29346443>.
8. Kaspar MB, Sterling RK. Mechanisms of liver disease in patients infected with HIV. *BMJ Open Gastroenterol*. 2017;4(1):e000166. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29119002>.
9. Melvin AJ, Warshaw M, Compagnucci A, et al. Hepatic, renal, hematologic, and inflammatory markers in HIV-infected children on long-term suppressive antiretroviral therapy. *J Pediatric Infect Dis Soc*. 2017;6(3):e109-e115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28903520>.
10. Cai J, Osikowicz M, Sebastiani G. Clinical significance of elevated liver transaminases in HIV-infected patients. *AIDS*. 2019;33(8):1267-1282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31008799>.
11. Tadesse BT, Foster BA, Kabeta A, et al. Hepatic and renal toxicity and associated factors among HIV-infected children on antiretroviral therapy: a prospective cohort study. *HIV Med*. 2019;20(2):147-156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30474906>.

### Hepatic Events and NRTIs

12. The European Pregnancy and Paediatric HIV Cohort Collaboration, (EPPICC) study group in EuroCoord. Safety of zidovudine/lamivudine scored tablets in children with HIV infection in Europe and Thailand. *Eur J of Clin Pharm*. 2017;73(4):463-468.

### Hepatic Events and NNRTIs

13. Phillips E, Bartlett JA, Sanne I, et al. Associations between HLA-DRB1\*0102, HLA-B\*5801, and hepatotoxicity during initiation of nevirapine-containing regimens

in South Africa. *J Acquir Immune Defic Syndr*. 2013;62(2):e55-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23328091>.

14. Sonderup MW, Maughan D, Gogela N, et al. Identification of a novel and severe pattern of efavirenz drug-induced liver injury in South Africa. *AIDS*. 2016;30(9):1483-1485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26959511>.
15. Bienczak A, Denti P, Cook A, et al. Determinants of virological outcome and adverse events in African children treated with paediatric nevirapine fixed-dose-combination tablets. *AIDS*. 2017;31(7):905-915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28060017>.

### **Hepatic Events and NRTIs plus NNRTIs**

16. Wu PY, Cheng CY, Liu CE, et al. Multicenter study of skin rashes and hepatotoxicity in antiretroviral-naive HIV-positive patients receiving non-nucleoside reverse-transcriptase inhibitor plus nucleoside reverse-transcriptase inhibitors in Taiwan. *PLoS One*. 2017;12(2):e0171596. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28222098>.

### **Hepatic Events and PIs including Indirect Hyperbilirubinemia**

17. Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naive and -experienced infants and children aged  $\geq 3$  months to  $< 6$  years. *J Int AIDS Soc*. 2015;18:19467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26066346>.
18. Rutstein RM, Samson P, Fenton T, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the pediatric AIDS clinical trials group protocol 1020A. *Pediatr Infect Dis J*. 2015;34:162-167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25232777>.
19. Crutchley RD, Guduru RC, Cheng AM. Evaluating the role of atazanavir/cobicistat and darunavir/cobicistat fixed-dose combinations for the treatment of HIV-1 infection. *HIV/AIDS*. 2016;8:47-65. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27022304>.
20. Cotton MF, Liberty A, Torres-Escobar I, et al. Safety and efficacy of atazanavir powder and ritonavir in HIV-1-infected infants and children from 3 months to  $< 11$  years of age: the PRINCE-2 study. *Pediatr Infect Dis J*. 2018;37(6):e149-e156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29206747>.
21. European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord. Safety of darunavir and atazanavir in HIV-infected children in Europe and Thailand. *Antivir Ther*. 2016;21(4):353-358. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26561496>.
22. Leger P, Chirwa S, Nwogu JN, et al. Race/ethnicity difference in the pharmacogenetics of bilirubin-related atazanavir discontinuation. *Pharmacogenet Genomics*. 2018;28(1):1-6. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29117017>.
23. Sevinsky H, Zaru L, Wang R, et al. Pharmacokinetics and Pharmacodynamics of Atazanavir in HIV-1-Infected Children Treated With Atazanavir Powder and Ritonavir: Combined Analysis of the PRINCE-1 and -2 Studies. *Pediatr Infect Dis J*. 2018;37(6):e157-e165. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29206748>.

### **HIV and Hepatitis B/C Coinfections**

24. Gowda C, Newcomb CW, Liu Q, et al. Risk of acute liver injury with antiretroviral therapy by viral hepatitis status. *Open Forum Infect Dis*. 2017;4(2):ofx012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28470014>.
25. Phung BC, Sogni P, Launay O. Hepatitis B and human immunodeficiency virus co-infection. *World J Gastroenterol*. 2014;20(46):17360-17367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25516647>.
26. European Paediatric HIV/HCV Co-infection Study Group in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) in EuroCoord. Coinfection

- with HIV and hepatitis C virus in 229 children and young adults living in Europe. *AIDS*. 2017;31(1):127-135. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27898593>.
27. Neukam K, Mira JA, Collado A, et al. Liver toxicity of current antiretroviral regimens in HIV-infected patients with chronic viral hepatitis in a real life setting: The HEPAVIR SEG-HEP Cohort. *PLoS One*. 2016;11(2):e0148104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26848975>.
28. Pokorska-Spiewak M, Stanska-Perka A, Popielska J, et al. Prevalence and predictors of liver disease in HIV-infected children and adolescents. *Sci Rep*. 2017;7(1):12309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28951598>.
29. Scott JA, Chew KW. Treatment optimization for HIV/HCV co-infected patients. *Ther Adv Infect Dis*. 2017;4(1):18-36. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28357062>.
30. Sohrab SS, Suhail M, Ali A, Qadri I, Harakeh S, Azhar EI. Consequence of HIV and HCV co-infection on host immune response, persistence and current treatment options. *Virusdisease*. 2018;29(1):19-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29607354>.

### **Nodular Regenerative Hyperplasia and Noncirrhotic Portal Hypertension**

31. Parikh ND, Martel-Laferriere V, Kushner T, et al. Clinical factors that predict noncirrhotic portal hypertension in HIV-infected patients: a proposed diagnostic algorithm. *J Infect Dis*. 2014;209(5):734-738. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23911709>.
32. Scherpbier HJ, Terpstra V, Pajkrt D, et al. Noncirrhotic portal hypertension in perinatally HIV-infected adolescents treated with didanosine-containing antiretroviral regimens in childhood. *Pediatr Infect Dis J*. 2016;35(8):e248-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27167116>.
33. Sood A, Castrejon M, Saab S. Human immunodeficiency virus and nodular regenerative hyperplasia of liver: A systematic review. *World J Hepatol*. 2014;6(1):55-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24653794>.

**Table 15f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated April 14, 2020; last reviewed April 14, 2020)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Insulin Resistance, Asymptomatic Hyperglycemia, DM<sup>a</sup></b>	ZDV, LPV/r, and possibly other PIs	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Weeks to months after beginning therapy</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Asymptomatic fasting hyperglycemia (which sometimes occurs in the setting of lipodystrophy), metabolic syndrome, or growth delay</li> <li>Symptomatic DM (rare)</li> </ul>	<p><b>Children:</b></p> <ul style="list-style-type: none"> <li>Insulin resistance, 6% to 12% (incidence is higher during puberty, 20% to 30%)</li> <li>Impaired fasting glucose, 0% to 7%</li> <li>Impaired glucose tolerance, 3% to 4%</li> <li>DM, 0.2 per 100 child-years</li> </ul>	<p><b>Risk Factors for Type 2 DM:</b></p> <ul style="list-style-type: none"> <li>Lipo-dystrophy</li> <li>Metabolic syndrome</li> <li>Family history of DM</li> <li>High BMI (obesity)</li> </ul>	<p><b>Prevention:</b></p> <ul style="list-style-type: none"> <li>Lifestyle modification</li> </ul> <p><b>Monitoring:</b></p> <ul style="list-style-type: none"> <li>Monitor for signs of DM, change in body habitus, and acanthosis nigricans.</li> <li>Obtain RPG levels at initiation of ART, 3–6 months after ART initiation, and yearly thereafter.</li> <li>In patients with an RPG <math>\geq 140</math> mg/dL, obtain FPG after an 8-hour fast and consider referring the patient to an endocrinologist.</li> </ul>	<p>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.</p> <p>If the patient is receiving ZDV, switch to TAF, TDF, or ABC.</p> <p><b>For Patients with Either an RPG <math>\geq 200</math> mg/dL Plus Symptoms of DM or an FPG <math>\geq 126</math> mg/dL:</b></p> <ul style="list-style-type: none"> <li>These patients meet diagnostic criteria for DM; consult an endocrinologist.</li> </ul> <p><b>For Patients with an FPG of 100–125 mg/dL:</b></p> <ul style="list-style-type: none"> <li>Impaired FPG suggests insulin resistance; consult an endocrinologist.</li> </ul> <p><b>For Patients with an FPG <math>&lt; 100</math> mg/dL:</b></p> <ul style="list-style-type: none"> <li>This FPG is normal, but a normal FPG does not exclude insulin resistance. Recheck FPG in 6–12 months.</li> </ul>

<sup>a</sup> 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).

*DM:* Often defined as either an FPG  $\geq 126$  mg/dL, an RPG  $\geq 200$  mg/dL in a patient with hyperglycemia symptoms, an HgbA1c of  $\geq 6.5\%$ , or a 2-hour PG  $\geq 200$  mg/dL in 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:** 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; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

## References

1. Aldrovandi GM, Lindsey JC, Jacobson DL, et al. Morphologic and metabolic abnormalities in vertically HIV-infected children and youth. *AIDS*. 2009;23(6):661-672. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19279441>.
2. American Diabetes Association. Classification and diagnosis of diabetes. *Diabetes Care*. 2016;39 Suppl 1:S13-22. Available at: <http://www.ncbi.nlm.nih.gov/>

[pubmed/26696675](http://pubmed/26696675).

3. Chantry CJ, Hughes MD, Alvero C, et al. Lipid and glucose alterations in HIV-infected children beginning or changing antiretroviral therapy. *Pediatrics*. 2008;122(1):e129-138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18519448>.
4. Dirajlal-Fargo S, Musiime V, Cook A, et al. Insulin resistance and markers of inflammation in HIV-infected Ugandan children in the CHAPAS-3 Trial. *Pediatr Infect Dis J*. 2017;36(8):761-767. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28067719>.
5. Espiau M, Yeste D, Noguera-Julian A, et al. Metabolic syndrome in children and adolescents living with HIV. *Pediatr Infect Dis J*. 2016;35(6):e171-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26910591>.
6. Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S36-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25629891>.
7. Geffner ME, Patel K, Miller TL, et al. Factors associated with insulin resistance among children and adolescents perinatally infected with HIV-1 in the pediatric HIV/AIDS cohort study. *Horm Res Paediatr*. 2011;76(6):386-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22042056>.
8. Hadigan C, Kattakuzhy S. Diabetes mellitus type 2 and abnormal glucose metabolism in the setting of human immunodeficiency virus. *Endocrinol Metab Clin North Am*. 2014;43(3):685-696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25169561>.
9. Hazra R, Hance LF, Monteiro JP, et al. Insulin resistance and glucose and lipid concentrations in a cohort of perinatally HIV-infected Latin American children. *Pediatr Infect Dis J*. 2013;32(7):757-759. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23360832>.
10. Innes S, Abdullah KL, Haubrich R, Cotton MF, Browne SH. High prevalence of dyslipidemia and insulin resistance in HIV-infected pre-pubertal African children on antiretroviral therapy. *Pediatr Infect Dis J*. 2016;35(1):e1-7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26421804>.
11. Loomba-Albrecht LA, Bregman T, Chantry CJ. Endocrinopathies in children infected with human immunodeficiency virus. *Endocrinol Metab Clin North Am*. 2014;43(3):807-828. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25169569>.
12. Mirani G, Williams PL, Chernoff M, et al. Changing trends in complications and mortality rates among US youth and young adults with HIV infection in the era of combination antiretroviral therapy. *Clin Infect Dis*. 2015;61(12):1850-1861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26270680>.
13. Non LR, Escota GV, Powderly WG. HIV and its relationship to insulin resistance and lipid abnormalities. *Transl Res*. 2017;183:41-56. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28068521>.
14. Paganella MP, Cohen RA, Harris DR, et al. Association of dyslipidemia and glucose abnormalities with antiretroviral treatment in a cohort of HIV-infected Latin American children. *J Acquir Immune Defic Syndr*. 2017;74(1):e1-e8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27570910>.
15. Patel K, Wang J, Jacobson DL, et al. Aggregate risk of cardiovascular disease among adolescents perinatally infected with the human immunodeficiency virus. *Circulation*. 2014;129(11):1204-1212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24366631>.
16. Samaras K. Prevalence and pathogenesis of diabetes mellitus in HIV-1 infection treated with combined antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009;50(5):499-505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19223782>.
17. Takemoto JK, Miller TL, Wang J, et al. Insulin resistance in HIV-infected youth is associated with decreased mitochondrial respiration. *AIDS*. 2017;31(1):15-23. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27755108>.
18. Geffner ME, Patel K, Jacobson DL, et al. Changes in insulin sensitivity over time and associated factors in HIV-infected adolescents. *AIDS*. 2018;32(5):613-622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29280758>.

**Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis**  
 (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lactic Acidosis	<p><b>NRTIs:</b></p> <ul style="list-style-type: none"> <li>ZDV</li> <li>Less likely with 3TC, FTC, ABC, TAF, and TDF</li> </ul> <p><b>Other Drugs:</b></p> <ul style="list-style-type: none"> <li>See the Risk Factors and Prevention/Monitoring columns for information regarding the toxicity of propylene glycol when LPV/r oral solution is used in neonates.</li> </ul>	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Generally after years of exposure</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Lactic acidosis may be clinically asymptomatic.</li> </ul> <p><i>Lactic Acidosis May Also Present with Insidious Onset of a Combination of Signs and Symptoms:</i></p> <ul style="list-style-type: none"> <li>Generalized fatigue, weakness, and myalgias</li> <li>Vague abdominal pain, weight loss, unexplained nausea, or vomiting</li> <li>Dyspnea</li> <li>Peripheral neuropathy</li> </ul> <p><b>Note:</b> Patients may present with acute multi-organ failure (e.g., fulminant hepatic failure, pancreatic failure, respiratory failure).</p>	<p>Lactic acidosis is associated with use of ddl and d4T. Cases are rare now that these NRTIs <b>are no longer recommended.</b></p> <p>3TC, FTC, ABC, TAF, and TDF are less likely to induce clinically significant mitochondrial dysfunction than ZDV.</p>	<p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>Female sex</li> <li>High BMI</li> <li>Chronic HCV infection</li> <li>African-American race</li> <li>Coadministration of TDF with metformin</li> <li>Overdose of propylene glycol</li> <li>CD4 count &lt;350 cells/mm<sup>3</sup></li> <li>Acquired riboflavin or thiamine deficiency</li> <li>Possibly pregnancy</li> </ul> <p><b>Preterm Infants or Any Neonates Who Have Not Attained a Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days:</b></p> <ul style="list-style-type: none"> <li>Exposure to propylene glycol, which is used as a diluent in LPV/r oral solution. A diminished ability to metabolize propylene glycol may lead to accumulation, increasing the risk of adverse events.</li> </ul>	<p><b>Prevention:</b></p> <ul style="list-style-type: none"> <li>Due to the presence of propylene glycol as a diluent, LPV/r oral solution <b>should not be used</b> in preterm neonates or any neonate who has not attained a postmenstrual age of 42 weeks and a postnatal age of ≥14 days.</li> <li>Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.</li> </ul> <p><b>Monitoring</b></p> <p><i>Asymptomatic Patients:</i></p> <ul style="list-style-type: none"> <li>Measurement of serum lactate <b>is not recommended.</b></li> </ul> <p><i>Patients with Clinical Signs or Symptoms Consistent with Lactic Acidosis:</i></p> <ul style="list-style-type: none"> <li>Obtain blood lactate level.<sup>a</sup></li> <li>Additional diagnostic evaluations should include serum bicarbonate, anion gap, and/or arterial blood gas; amylase and lipase; serum albumin; and hepatic transaminases.</li> </ul>	<p><b>For Patients with Lactate 2.1–5.0 mmol/L (Confirmed with a Second Test):</b></p> <ul style="list-style-type: none"> <li>Consider discontinuing all ARV drugs temporarily while conducting additional diagnostic workup.</li> </ul> <p><b>For Patients with Lactate &gt;5.0 mmol/L (Confirmed With a Second Test)<sup>b</sup> or &gt;10.0 mmol/L (Any One Test):</b></p> <ul style="list-style-type: none"> <li>Discontinue all ARV drugs.</li> <li>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).</li> </ul> <p><b>Anecdotal (Unproven) Supportive Therapies:</b></p> <ul style="list-style-type: none"> <li>Administer bicarbonate infusions, THAM, high doses of thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C)</li> </ul> <p>Following the resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen. Institute a revised NRTI-containing regimen with caution, using NRTIs that are less likely to induce mitochondrial dysfunction (ABC, TAF, TDF, FTC or 3TC). Lactate should be monitored monthly for ≥3 months.</p>

## Table 15g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

<sup>a</sup> 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.

<sup>b</sup> Management can be initiated before receiving the results of the confirmatory test.

**Key:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; 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

### References

#### General Reviews

1. Fortuny C, Deya-Martinez A, Chiappini E, Galli L, de Martino M, Noguera-Julian A. Metabolic and renal adverse effects of antiretroviral therapy in HIV-infected children and adolescents. *Pediatr Infect Dis J*. 2015;34(5 Suppl 1):S36-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25629891>.
2. Margolis AM, Heverling H, Pham PA, Stolbach A. A review of the toxicity of HIV medications. *J Med Toxicol*. 2014;10(1):26-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23963694>.
3. Tukei VJ, Asiimwe A, Maganda A, et al. Safety and tolerability of antiretroviral therapy among HIV-infected children and adolescents in Uganda. *J Acquir Immune Defic Syndr*. 2012;59(3):274-280. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22126740>.
4. Bartlett AW, Mohamed TJ, Sudjaritruk T, et al. Disease- and treatment-related morbidity in adolescents with perinatal HIV infection in Asia. *Pediatr Infect Dis J*. 2019;38(3):287-292. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30281549>.
5. Tshamala HK, Aketi L, Tshibassu PM, et al. The lipodystrophy syndrome in HIV-infected children under antiretroviral therapy: a first report from the Central Africa. *Int J Pediatr*. 2019;2019:7013758. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30941184>.
6. Smith ZR, Horng M, Rech MA. Medication-induced hyperlactatemia and lactic acidosis: a systematic review of the literature. *Pharmacotherapy*. 2019;39(9):946-963. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31361914>.

#### Risk Factors

8. Aperis G, Paliouras C, Zervos A, Arvanitis A, Alivannis P. Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection. *J Ren Care*. 2011;37(1):25-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21288314>.
9. Lopinavir/ritonavir (Kaletra) [package insert]. Food and Drug Administration. 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/021251s055\\_021906s050lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021251s055_021906s050lbl.pdf).
10. Firnhaber C, Smeaton LM, Grinsztejn B, et al. Differences in antiretroviral safety and efficacy by sex in a multinational randomized clinical trial. *HIV Clin Trials*. 2015;16(3):89-99. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25979186>.
11. Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PLoS One*. 2017;12(2):e0169762. Available at: <https://>

[www.ncbi.nlm.nih.gov/pubmed/28192529](http://www.ncbi.nlm.nih.gov/pubmed/28192529).

12. Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. *J Pediatr Pharmacol Ther.* 2014;19(4):277-282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25762872>.
13. Mamiafo CT, Moor VJ, Nansseu JR, Pieme CA, Tayou C, Yonkeu JN. Hyperlactatemia in a group of HIV patients living in Yaounde-Cameroon. *AIDS Res Ther.* 2014;11(1):2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24428886>.
14. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS One.* 2011;6(4):e18736. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21494566>.
15. Moren C, Noguera-Julian A, Garrabou G, et al. Mitochondrial evolution in HIV-infected children receiving first- or second-generation nucleoside analogues. *J Acquir Immune Defic Syndr.* 2012;60(2):111-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22362155>.
16. Tetteh RA, Nartey ET, Lartey M, et al. Association between the occurrence of adverse drug events and modification of first-line highly active antiretroviral therapy in Ghanaian HIV patients. *Drug Safety.* 2016;39(11):1139-1149. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27638659>.
17. Wester CW, Eden SK, Shepherd BE, et al. Risk factors for symptomatic hyperlactatemia and lactic acidosis among combination antiretroviral therapy-treated adults in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses.* 2012;28(8):759-765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22540188>.

#### Monitoring and Management

18. Barlow-Mosha L, Eckard AR, McComsey GA, Musoke PM. Metabolic complications and treatment of perinatally HIV-infected children and adolescents. *J Int AIDS Soc.* 2013;16:18600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782481>.
19. Claessens YE, Cariou A, Monchi M, et al. Detecting life-threatening lactic acidosis related to nucleoside-analog treatment of human immunodeficiency virus-infected patients, and treatment with L-carnitine. *Crit Care Med.* 2003;31(4):1042-1047. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12682470>.
20. Kraut JA, Madias NE. Lactic acidosis. *N Engl J Med.* 2014;371(24):2309-2319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25494270>.
21. Marfo K, Garala M, Kvetan V, Gasperino J. Use of Tris-hydroxymethyl aminomethane in severe lactic acidosis due to highly active antiretroviral therapy: a case report. *J Clin Pharm Ther.* 2009;34(1):119-123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19125910>.
22. Jung B, Martinez M, Claessens YE, et al. Diagnosis and management of metabolic acidosis: guidelines from a French expert panel. *Ann Intensive Care.* 2019;9(1):92. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31418093>.

**Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Lipodystrophy (Fat Maldistribution)</b> General Information	See below for specific associations.	<b>Onset:</b> <ul style="list-style-type: none"> <li>Increase in trunk and limb fat are the first sign; peripheral fat wasting may not appear for 12–24 months after ART initiation.</li> </ul>	Frequency is low (<5%) with current regimens.	Genetic predisposition Puberty HIV-associated inflammation Older age Longer duration of ART Body habitus	<b>Prevention:</b> <ul style="list-style-type: none"> <li>Initiate a calorically appropriate, low-fat diet and an exercise regimen.</li> </ul> <b>Monitoring:</b> <ul style="list-style-type: none"> <li>BMI measurement</li> <li>Waist circumference and waist-hip ratio</li> </ul>	Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs.  Improvement in fat maldistribution can vary following a regimen change. Improvement may occur after several months or years, or it may not occur at all.
<b>Central Lipohypertrophy</b> or <b>Lipo-accumulation</b>	Can occur in the absence of ART, but these conditions are most often associated with the use of PIs and EFV.	<b>Presentation:</b> <ul style="list-style-type: none"> <li>Central fat accumulation with increased abdominal girth, which may include a dorsocervical fat pad (buffalo hump). Gynecomastia may occur in males or breast hypertrophy may occur in females, particularly with the use of EFV.</li> </ul>	Frequency is low (<5%) with current regimens.	Obesity before initiation of therapy Sedentary lifestyle	<b>Prevention:</b> <ul style="list-style-type: none"> <li>Initiate a calorically appropriate, low-fat diet and an exercise regimen.</li> </ul> <b>Monitoring:</b> <ul style="list-style-type: none"> <li>BMI measurement</li> <li>Waist circumference and waist-hip ratio</li> </ul>	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training).  Recommend smoking cessation (if applicable) to decrease future CVD risk.  Consider using an INSTI instead of a PI or EFV, although some INSTIs may be associated with generalized weight gain (see below).  <b>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:</b> <ul style="list-style-type: none"> <li>Recombinant human growth hormone</li> <li>Growth hormone-releasing hormone</li> <li>Metformin</li> <li>Thiazolidinediones</li> <li>Recombinant human leptin</li> <li>Anabolic steroids</li> <li>Liposuction</li> </ul>

**Table 15h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophies and Weight Gain** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Facial/Peripheral Lipodystrophy</b>	Most cases are associated with the use of ZDV, a thymidine analogue NRTI.	<b>Presentation:</b> <ul style="list-style-type: none"> <li>• 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 lipodystrophy from HIV-associated wasting.</li> </ul>	Frequency is low (<5%) with current regimens.	Underweight before ART initiation	<b>Prevention:</b> <ul style="list-style-type: none"> <li>• Limit the use of ZDV.</li> </ul> <b>Monitoring:</b> <ul style="list-style-type: none"> <li>• Patient self-report and physical examination are the most sensitive methods of monitoring lipodystrophy.</li> </ul>	Replace ZDV with another NRTI when possible.  <b>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:</b> <ul style="list-style-type: none"> <li>• Injections of poly-L-lactic acid</li> <li>• Recombinant human leptin</li> <li>• Autologous fat transplantation</li> <li>• Thiazolidinediones</li> </ul>
<b>Weight Gain</b>	Significant weight gain may occur with all ARV regimens, but it appears to be more pronounced with DTG, BIC, and TAF.	Gradual weight gain after initiating ARV drugs is common with all currently used regimens. The mechanism for weight gain is unclear and is under investigation.	Rate of development of obesity is unclear.	<b>In Adults:</b> <ul style="list-style-type: none"> <li>• Low pre-treatment BMI</li> <li>• Older age</li> <li>• Female sex</li> <li>• Black race</li> </ul> Risk factors for weight gain have not yet been evaluated in infants and children.	<b>Prevention:</b> <ul style="list-style-type: none"> <li>• Initiate a calorically appropriate, low-fat diet and an exercise regimen.</li> </ul> <b>Monitoring:</b> <ul style="list-style-type: none"> <li>• BMI measurement</li> <li>• Waist circumference and waist-hip ratio</li> </ul>	Counsel patient on lifestyle modification and dietary interventions (e.g., maintaining a calorically appropriate, healthy diet that is low in saturated fats and simple carbohydrates, and starting an exercise regimen, especially strength training).

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

## References

See the archived version of [Supplement III, February 23, 2009, Pediatric Guidelines](#) on the [AIDSinfo website](#) for a more complete discussion and reference list.

### General Reviews

1. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of African-American, European-American, and Mexican-American children and adolescents. *J Pediatr*. 2004;145(4):439-444. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15480363>.
2. Alves Junior CAS, de Lima LRA, de Souza MC, Silva DAS. Anthropometric measures associated with fat mass estimation in children and adolescents with HIV.

- Appl Physiol Nutr Metab.* 2019;44(5):493-498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30286302>.
3. Kumar S, Samaras K. The impact of weight gain during HIV treatment on risk of pre-diabetes, diabetes mellitus, cardiovascular disease, and mortality. *Front Endocrinol (Lausanne)*. 2018;9:705. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30542325>.
  4. Innes S, Cotton MF, Haubrich R, et al. High prevalence of lipoatrophy in pre-pubertal South African children on antiretroviral therapy: a cross-sectional study. *BMC Pediatr.* 2012;12:183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23176441>.
  5. Prendergast AJ. Complications of long-term antiretroviral therapy in HIV-infected children. *Arch Dis Child.* 2013;98(4):245-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23413313>.
  6. Arbeitman LE, O'Brien RC, Somarriba G, et al. Body mass index and waist circumference of HIV-infected youth in a Miami cohort: comparison to local and national cohorts. *J Pediatr Gastroenterol Nutr.* 2014;59(4):449-454. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24709829>.
  7. Nduka CU, Uthman OA, Kimani PK, Stranges S. Body fat changes in people living with HIV on antiretroviral therapy. *AIDS Rev.* 2016;18(4):198-211. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27438580>.
  8. Kenny J, Doerholt K, Gibb DM, Judd A, Collaborative HIVPSSC. Who gets severe gynecomastia among HIV-infected children in the United Kingdom and Ireland? *Pediatr Infect Dis J.* 2017;36(3):307-310. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27879556>.
  9. Ramteke SM, Shiau S, Foca M, et al. Patterns of growth, body composition, and lipid profiles in a South African cohort of human immunodeficiency virus-infected and uninfected children: a cross-sectional study. *J Pediatric Infect Dis Soc.* 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28481997>.
  10. Sharma TS, Somarriba G, Arheart KL, et al. Longitudinal changes in body composition by dual-energy radiograph absorptiometry among perinatally HIV-infected and HIV-uninfected youth: increased risk of adiposity among HIV-infected female youth. *Pediatr Infect Dis J.* 2018;37(10):1002-1007. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29474262>.
  11. de Castro JAC, de Lima LRA, Silva DAS. Accuracy of octa-polar bioelectrical impedance analysis for the assessment of total and appendicular body composition in children and adolescents with HIV: comparison with dual energy X-ray absorptiometry and air displacement plethysmography. *J Hum Nutr Diet.* 2018;31(2):276-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28799180>.
  12. Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? *J Virus Erad.* 2019;5(1):41-43. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30800425>.
  13. Taramasso L, Ricci E, Menzaghi B, et al. Weight gain: a possible side effect of all antiretrovirals. *Open Forum Infect Dis.* 2017;4(4):ofx239. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29255735>.

#### Associated ARVs/Etiology

14. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS.* 2009;23(9):1109-1118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19417580>.
15. Hulgán T, Tebas P, Canter JA, et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy. *J Infect Dis.* 2008;197(6):858-866. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18419350>.
16. McComsey GA, Libutti DE, O'Riordan M, et al. Mitochondrial RNA and DNA alterations in HIV lipoatrophy are linked to antiretroviral therapy and not to HIV

infection. *Antivir Ther.* 2008;13(5):715-722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18771055>.

17. Arrive E, Viard JP, Salanave B, et al. Metabolic risk factors in young adults infected with HIV since childhood compared with the general population. *PLoS One.* 2018;13(11):e0206745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30408056>.
18. Arpadi S, Shiau S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child.* 2013;98(4):258-264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23220209>.
19. Cohen S, Innes S, Geelen SP, et al. Long-term changes of subcutaneous fat mass in HIV-infected children on antiretroviral therapy: a retrospective analysis of longitudinal data from two pediatric HIV-cohorts. *PLoS One.* 2015;10(7):e0120927. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26148119>.
20. Dos Reis LC, de Carvalho Rondo PH, de Sousa Marques HH, Jose Segri N. Anthropometry and body composition of vertically HIV-infected children and adolescents under therapy with and without protease inhibitors. *Public Health Nutr.* 2015;18(7):1255-1261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25115797>.
21. McComsey GA, Moser C, Currier J, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. *Clin Infect Dis.* 2016;62(7):853-862. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26797215>.
22. Moure R, Domingo P, Gallego-Escuredo JM, et al. Impact of elvitegravir on human adipocytes: Alterations in differentiation, gene expression and release of adipokines and cytokines. *Antiviral Res.* 2016;132:59-65. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27216995>.
23. Innes S, Harvey J, Collins IJ, Cotton MF, Judd A. Lipoatrophy/lipohypertrophy outcomes after antiretroviral therapy switch in children in the UK/Ireland. *PLoS One.* 2018;13(4):e0194132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29617438>.
24. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in waist circumference in HIV-infected individuals initiating a raltegravir or protease inhibitor regimen: effects of sex and race. *Open Forum Infect Dis.* 2018;5(11):ofy201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30465010>.
25. Norwood J, Turner M, Bofill C, et al. Brief Report: Weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr.* 2017;76(5):527-531. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28825943>.
26. Bourgi K, Rebeiro PF, Turner M, et al. Greater weight gain in treatment naive persons starting dolutegravir-based antiretroviral therapy. *Clin Infect Dis.* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31100116>.
27. Gomez M, Seybold U, Roeder J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015–2017. *Infection.* 2019;47(1):95-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30269210>.
28. Eckard AR, McComsey GA. Weight gain and integrase inhibitors. *Curr Opin Infect Dis.* 2020;33(1):10-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31789693>.

## Management

29. Hadigan C. Peroxisome proliferator-activated receptor gamma agonists and the treatment of HIV-associated lipoatrophy: unraveling the molecular mechanism of their shortcomings. *J Infect Dis.* 2008;198(12):1729-1731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18954262>.
30. Lindegaard B, Hansen T, Hvid T, et al. The effect of strength and endurance training on insulin sensitivity and fat distribution in human immunodeficiency virus-

- infected patients with lipodystrophy. *J Clin Endocrinol Metab.* 2008;93(10):3860-3869. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18628529>.
31. Lo J, You SM, Canavan B, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. *JAMA.* 2008;300(5):509-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18677023>.
  32. Tebas P, Zhang J, Hafner R, et al. Peripheral and visceral fat changes following a treatment switch to a non-thymidine analogue or a nucleoside-sparing regimen in HIV-infected subjects with peripheral lipoatrophy: results of ACTG A5110. *J Antimicrob Chemother.* 2009;63(5):998-1005. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19299471>.
  33. Falutz J, Mamputu JC, Potvin D, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab.* 2010;95(9):4291-4304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20554713>.
  34. Ferrer E, del Rio L, Martinez E, et al. Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. *AIDS Res Hum Retroviruses.* 2011;27(10):1061-1065. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21166602>.
  35. Negredo E, Miro O, Rodriguez-Santiago B, et al. Improvement of mitochondrial toxicity in patients receiving a nucleoside reverse-transcriptase inhibitor-sparing strategy: results from the Multicenter Study with Nevirapine and Kaletra (MULTINEKA). *Clin Infect Dis.* 2009;49(6):892-900. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19663689>.
  36. Raboud JM, Diong C, Carr A, et al. A meta-analysis of six placebo-controlled trials of thiazolidinedione therapy for HIV lipoatrophy. *HIV Clin Trials.* 2010;11(1):39-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20400410>.
  37. Sheth SH, Larson RJ. The efficacy and safety of insulin-sensitizing drugs in HIV-associated lipodystrophy syndrome: a meta-analysis of randomized trials. *BMC Infect Dis.* 2010;10:183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20573187>.
  38. Tungsiripat M, Bejjani DE, Rizk N, et al. Rosiglitazone improves lipoatrophy in patients receiving thymidine-sparing regimens. *AIDS.* 2010;24(9):1291-1298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20453626>.
  39. Spoulou V, Kanaka-Gantenbein C, Bathrellou I, et al. Monitoring of lipodystrophic and metabolic abnormalities in HIV-1 infected children on antiretroviral therapy. *Hormones.* 2011;10(2):149-155. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21724540>.
  40. Young L, Wohl DA, Hyslop WB, Lee YZ, Napravnik S, Wilkin A. Effects of raltegravir combined with tenofovir/emtricitabine on body shape, bone density, and lipids in African-Americans initiating HIV therapy. *HIV Clin Trials.* 2015;16(5):163-169. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26249671>.

**Table 15i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects**  
 (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Urolithiasis/ Nephrolithiasis</b>	ATV  DRV causes crystalluria, but it is not associated with nephrolithiasis.	<b>Onset:</b> • Weeks to months after starting therapy  <b>Clinical Findings:</b> • Crystalluria • Hematuria • Pyuria • Flank pain • Increased creatinine levels in some cases	ATV-related nephrolithiasis occurs in <10% of patients and has been reported after stopping ATV.	In adults, elevated urine pH (>5.7)  The risk factors in children are unknown.	<b>Prevention:</b> • Maintain adequate hydration.  <b>Monitoring:</b> • Obtain urinalysis at least every 6–12 months.	Provide adequate hydration and pain control. Consider using another ARV drug in place of ATV.
<b>Renal Dysfunction</b>	TDF	<b>Onset:</b> • Variable; in adults, renal dysfunction may occur weeks to months after initiating therapy. • Hypophosphatemia appears at a median of 18 months. • Glucosuria may occur after 1 year of therapy. • Abnormal urine protein/osmolality ratio may be an early indicator.  <b>Presentation</b> <i>More Common:</i> • Increased serum creatinine levels, proteinuria, normoglycemic glucosuria • Increased urinary protein/creatinine ratio and albumin/creatinine ratio • Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain or muscle weakness  <i>Less Common:</i> • Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria	<b>Adults:</b> • Approximately 2% of adults experience increased serum creatinine levels. • Approximately 0.5% of adults experience severe renal complications.  <b>Children:</b> • Approximately 4% of children experience hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy and advanced HIV infection.	<b>Risk May Increase in Children with the Following Characteristics:</b> • Aged >6 years • Black race, Hispanic/Latino ethnicity • Advanced HIV infection • Hypertension • Diabetes • Concurrent use of PIs (especially LPV/r) and preexisting renal dysfunction • Longer duration of TDF treatment • The presence of the apolipoprotein L1 variants G1 and G2 appears to increase the risk of renal abnormality in children with HIV. These alleles are more common in persons of black descent.	Monitor urine protein, urine glucose and serum creatinine at 3-month to 6-month intervals. Some Panel members routinely monitor serum phosphate levels in patients who are taking TDF.  Measure serum phosphate if the patient experiences persistent proteinuria 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**  
 (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Elevation in Serum Creatinine	DTG, COBI, RPV, <b>BIC</b>	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Within a month of starting treatment</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in serum creatinine levels without a true change in eGFR.</li> </ul>	<p>Common</p> <p>Clinicians need to distinguish between a true change in eGFR and other causes. A true change may be associated with other medical conditions, the continuing rise of serum creatinine levels over time, and albuminuria.</p>	The risk factors in children are unknown.	Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or if increases continue over time.	<p>No need to change therapy.</p> <p>Reassure the patient about the benign nature of the laboratory abnormality.</p>

**Key:** ARV = antiretroviral; ATV = atazanavir; **BIC = bicitegravir**; 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

## References

1. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J.* 2009;28(7):619-625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19561425>.
2. Judd A, Boyd KL, Stohr W, et al. Effect of tenofovir disoproxil fumarate on risk of renal abnormality in HIV-1-infected children on antiretroviral therapy: a nested case-control study. *AIDS.* 2010;24(4):525-534. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20139752>.
3. Nachman SA, Chernoff M, Gona P, et al. Incidence of noninfectious conditions in perinatally HIV-infected children and adolescents in the HAART era. *Arch Pediatr Adolesc Med.* 2009;163(2):164-171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19188649>.
4. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United kingdom and Ireland. *Pediatr Infect Dis J.* 2009;28(3):204-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19209091>.
5. Soler-Palacin P, Melendo S, Noguera-Julian A, et al. Prospective study of renal function in HIV-infected pediatric patients receiving tenofovir-containing HAART regimens. *AIDS.* 2011;25(2):171-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21076275>.
6. van Rossum AM, Dieleman JP, Fraaij PL, et al. Indinavir-associated asymptomatic nephrolithiasis and renal cortex atrophy in two HIV-1 infected children. *AIDS.* 2001;15(13):1745-1747. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11546957>.
7. Purswani M, Patel K, Kopp JB, et al. Tenofovir treatment duration predicts proteinuria in a multiethnic United States cohort of children and adolescents with perinatal HIV-1 infection. *Pediatr Infect Dis J.* 2013;32(5):495-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23249917>.
8. Nishijima T, Hamada Y, Watanabe K, et al. Ritonavir-boosted darunavir is rarely associated with nephrolithiasis compared with ritonavir-boosted atazanavir in HIV-infected patients. *PLoS One.* 2013;8(10):e77268. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24130871>.

9. de Lastours V, Ferrari Rafael De Silva E, Daudon M, et al. High levels of atazanavir and darunavir in urine and crystalluria in asymptomatic patients. *J Antimicrob Chemother.* 2013;68(8):1850-1856. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23599359>.
10. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr.* 2012;61(1):32-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22732469>.
11. Lim Y, Lyall H, Foster C. Tenofovir-associated nephrotoxicity in children with perinatally-acquired HIV infection: a single-centre cohort study. *Clin Drug Investig.* 2015;35(5):327-333. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25861908>.
12. Samarawickrama A, Cai M, Smith ER, et al. Simultaneous measurement of urinary albumin and total protein may facilitate decision-making in HIV-infected patients with proteinuria. *HIV Med.* 2012;13(9):526-532. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22413854>.
13. Marcelin JR, Berg ML, Tan EM, Amer H, Cummins NW, Rizza SA. Is abnormal urine protein/osmolality ratio associated with abnormal renal function in patients receiving tenofovir disoproxil fumarate? *PLoS One.* 2016;11(2):e0149562. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26872144>.
14. Lin KY, Liao SH, Liu WC, et al. Cholelithiasis and sephrolithiasis in HIV-positive patients in the era of combination antiretroviral therapy. *PLoS One.* 2015;10(9):e0137660. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26360703>.
15. Bunupuradah T, Phupitakphol T, Sophonphan J, et al. Prevalence of persistent renal dysfunction in perinatally HIV-infected Thai adolescents. *Pediatr Infect Dis J.* 2018;37(1):66-70. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28719505>.
16. Purswani MU, Patel K, Winkler CA, et al. Brief report: APOL1 renal risk variants are associated with chronic kidney disease in children and youth With perinatal HIV infection. *J Acquir Immune Defic Syndr.* 2016;73(1):63-68. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27035887>.
17. Soares DS, Cavalcante MG, Ribeiro SM, et al. Acute kidney injury in HIV-infected children: comparison of patients according to the use of highly active antiretroviral therapy. *J Pediatr (Rio J).* 2016;92(6):631-637. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27542916>.
18. Brunel V, Massy N, Malval B. Atazanavir urolithiasis without recent intake of atazanavir. *Ann Biol Clin (Paris).* 2019;77(4):459-460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31418708>.
19. Ekulu PM, Nkoy AB, Betukumesu DK, et al. APOL1 risk genotypes are associated with early kidney damage in children in sub-saharan Africa. *Kidney Int Rep.* 2019;4(7):930-938. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31317115>.
20. Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. *AIDS.* 2019;33(9):1455-1465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30932951>.

**Table 15j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis** (Last updated April 14, 2020; last reviewed April 14, 2020)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Osteopenia and Osteoporosis</b>	Any ART regimen  <b>Specific Agents of Concern:</b> • TDF, especially when used in a regimen that includes a boosting agent (i.e., RTV, COBI) • PIs	<b>Onset:</b> • Any age; decrease in BMD is usually seen soon after initiating ART.  <b>Presentation:</b> • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., a fracture with minimal trauma).	<b>BMD z-Score Less Than -2.0:</b> • <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	<b>Prevention:</b> • 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.  <b>Monitoring:</b> • Assess nutritional intake (calcium, vitamin D, and total calories). • Strongly consider measuring serum 25-OH-vitamin D levels, particularly in patients who are taking ARV drugs of concern. <sup>a</sup> • DXA is rarely indicated. <sup>b</sup>	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 unboosted INSTI whenever possible).  Treat patient with vitamin D3 to raise serum 25-OH-vitamin D concentrations to >30 ng/mL. There is no clear benefit to administering daily supplemental vitamin D3 doses that are >4,000 IU. If patients are receiving a daily dose of vitamin D3 that is >4,000 IU, consider monitoring levels of 25-OH-vitamin D.  An increase in BMD was seen in one study that evaluated the use of alendronate in youth with HIV. However, the role of bisphosphonates in managing osteopenia and osteoporosis in children with HIV has not been established.

<sup>a</sup> 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.

<sup>b</sup> 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. DXA scanning could be considered for youth who are receiving TDF along with additional medications which affect bone density and for children with indications that are not uniquely related to HIV infection (such as cerebral palsy).

**Key:** 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; ng = nanogram; PI = protease inhibitor; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

## References

1. Arpadi SM, Shiao S, Strehlau R, et al. Efavirenz is associated with higher bone mass in South African children with HIV. *AIDS*. 2016;30(16):2459-2467. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27427876>.
2. Aupibul L, Cressey TR, Sricharoenchai S, et al. Efficacy, safety and pharmacokinetics of tenofovir disoproxil fumarate in virologic-suppressed HIV-infected children using weight-band dosing. *Pediatr Infect Dis J*. 2015;34(4):392-397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25760566>.
3. Bachrach LK, Gordon CM, Section On E. Bone densitometry in children and adolescents. *Pediatrics*. 2016;138(4). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27669735>.
4. Bunders MJ, Frinking O, Scherpbier HJ, et al. Bone mineral density increases in HIV-infected children treated with long-term combination antiretroviral therapy. *Clin Infect Dis*. 2013;56(4):583-586. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23097583>.
5. DiMiglio LA, Wang J, Siberry GK, et al. Bone mineral density in children and adolescents with perinatal HIV infection. *AIDS*. 2013;27(2):211-220. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23032412>.
6. Eckard AR, Mora S. Bone health in HIV-infected children and adolescents. *Curr Opin HIV AIDS*. 2016;11(3):294-300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26890208>.
7. Eckard AR, O'Riordan MA, Rosebush JC, et al. Effects of vitamin D supplementation on bone mineral density and bone markers in HIV-infected youth. *J Acquir Immune Defic Syndr*. 2017;76(5):539-546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28902705>.
8. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. 2006;118(3):e711-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16923923>.
9. Havens PL, Stephensen CB, Van Loan MD, et al. Vitamin D3 supplementation increases spine bone mineral density in adolescents and young adults with human immunodeficiency virus infection being treated with tenofovir disoproxil fumarate: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2018;66(2):220-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29020329>.
10. Huang JS, Hughes MD, Riddler SA, Haubrich RH, AIDS Clinical Trials Group A. Study Team. Bone mineral density effects of randomized regimen and nucleoside reverse transcriptase inhibitor selection from ACTG A5142. *HIV Clin Trials*. 2013;14(5):224-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24144899>.
11. Kalkwarf HJ, Zemel BS, Gilsanz V, et al. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab*. 2007;92(6):2087-2099. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17311856>.
12. LaFleur J, Bress AP, Myers J, et al. Tenofovir-associated bone adverse outcomes among a US national historical cohort of HIV-infected veterans: risk modification by concomitant antiretrovirals. *Infect Dis Ther*. 2018;7(2):293-308. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29492905>.
13. Lima LR, Silva RC, Giuliano Ide C, Sakuno T, Brincas SM, Carvalho AP. Bone mass in children and adolescents infected with human immunodeficiency virus. *Jornal de Pediatria*. 2013;89(1):91-99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23544816>.
14. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16(1):43-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26538525>.
15. Okonkwo RI, Weidmann AE, Effa EE. Renal and bone adverse effects of a tenofovir-based regimen in the treatment of HIV-infected children: a systematic review. *Drug Saf*. 2016;39(3):209-218. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26692394>.

16. Overton ET, Chan ES, Brown TT, et al. Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: a randomized trial. *Ann Intern Med*. 2015;162(12):815-824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26075752>.
17. Palchetti CZ, Szejnfeld VL, de Menezes Succi RC, et al. Impaired bone mineral accrual in prepubertal HIV-infected children: a cohort study. *Braz J Infect Dis*. 2015;19(6):623-630. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26477385>.
18. Puthanakit T, Saksawad R, Bunupuradah T, et al. Prevalence and risk factors of low bone mineral density among perinatally HIV-infected Thai adolescents receiving antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012;61(4):477-483. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22918157>.
19. Puthanakit T, Siberry GK. Bone health in children and adolescents with perinatal HIV infection. *J Int AIDS Soc*. 2013;16:18575. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782476>.
20. Puthanakit T, Wittawatmongkol O, Poomlek V, et al. Effect of calcium and vitamin D supplementation on bone mineral accrual among HIV-infected Thai adolescents with low bone mineral density. *J Virus Erad*. 2018;4(1):6-11. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29568546>.
21. Siberry GK, Li H, Jacobson D, Pediatric AIDS Clinical Trials Group C. Study. Fracture risk by HIV infection status in perinatally HIV-exposed children. *AIDS Res Hum Retroviruses*. 2012;28(3):247-250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22471877>.
22. Tebas P, Kumar P, Hicks C, et al. Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naïve adults over 144 weeks. *AIDS*. 2015;29(18):2459-2464. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26355674>.
23. Schall JI, Hediger ML, Zemel BS, Rutstein RM, Stallings VA. Comprehensive safety monitoring of 12-month daily 7000-IU vitamin D3 supplementation in human immunodeficiency virus-infected children and young adults. *JPEN J Parenter Enteral Nutr*. 2016;40(7):1057-1063. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26160254>.
24. Dougherty KA, Schall JI, Zemel BS, et al. Safety and efficacy of high-dose daily vitamin D3 supplementation in children and young adults infected with human immunodeficiency virus. *J Pediatric Infect Dis Soc*. 2014;3(4):294-303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26625449>.
25. Negro E, Langohr K, Bonjoch A, et al. High risk and probability of progression to osteoporosis at 10 years in HIV-infected individuals: the role of PIs. *J Antimicrob Chemother*. 2018;73(9):2452-2459. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29860519>.
26. Havens PL, Long D, Schuster GU, et al. Tenofovir disoproxil fumarate appears to disrupt the relationship of vitamin D and parathyroid hormone. *Antivir Ther*. 2018;23(7):623-628. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30260797>.
27. Van Welzen BJ, Thielen MAJ, Mudrikova T, Arends JE, Hoepelman AIM. Switching tenofovir disoproxil fumarate to tenofovir alafenamide results in a significant decline in parathyroid hormone levels: uncovering the mechanism of tenofovir disoproxil fumarate-related bone loss? *AIDS*. 2019;33(9):1531-1534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31021851>.
28. Penner J, Ferrand RA, Richards C, Ward KA, Burns JE, Gregson CL. The impact of vitamin D supplementation on musculoskeletal health outcomes in children, adolescents, and young adults living with HIV: A systematic review. *PLoS One*. 2018;13(11):e0207022. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30439968>.
29. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21646368>.
30. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21118827>.
31. Burt LA, Billington EO, Rose MS, Raymond DA, Hanley DA, Boyd SK. Effect of high-dose vitamin D supplementation on volumetric bone density and bone strength: a randomized clinical trial. *JAMA*. 2019;322(8):736-745. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31454046>.

**Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated April 14, 2020; last reviewed April 14, 2020) (1 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Rash</b>	Any ARV drug can cause rash.	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• First few days to weeks after starting new ARV drug(s)</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Most rashes are mild-to-moderate, diffuse maculopapular eruptions.</li> </ul> <p><b>Note:</b> A rash can be the initial manifestation of systemic hypersensitivity (see the SJS/TEN/EM major and HSR sections below).</p>	<p><b>Common (&gt;10%):</b></p> <ul style="list-style-type: none"> <li>• EFV</li> <li>• ETR</li> <li>• FTC</li> <li>• NVP</li> </ul> <p><b>Less Common (5% to 10%):</b></p> <ul style="list-style-type: none"> <li>• ABC</li> <li>• ATV</li> <li>• DRV</li> <li>• TDF</li> </ul> <p><b>Unusual (2% to 4%):</b></p> <ul style="list-style-type: none"> <li>• LPV/r</li> <li>• MVC</li> <li>• RAL</li> <li>• RPV</li> </ul>	<p>Sulfonamide allergy is a risk factor for rash in patients who are taking PIs that contain a sulfonamide moiety (i.e., DRV).</p> <p>Polymorphisms in CYP2B6 and multiple HLA loci are associated with an increased risk of rash in patients who are taking NVP.</p>	<p><b>When Starting NVP or Restarting NVP After Interruptions of &gt;14 Days:</b></p> <ul style="list-style-type: none"> <li>• Utilize once-daily lead-in dosing.<sup>a</sup> This may not be necessary in children aged &lt;2 years.<sup>b</sup></li> <li>• Avoid the use of systemic corticosteroids during NVP dose escalation.</li> <li>• Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction.</li> </ul>	<p><b>Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:</b></p> <ul style="list-style-type: none"> <li>• Most rashes will resolve without intervention; ARV drugs can be continued while monitoring.<sup>a</sup></li> <li>• Antihistamines may provide some relief.</li> </ul> <p><b>Severe Rash and/or Rash Accompanied by Systemic Symptoms:</b></p> <ul style="list-style-type: none"> <li>• Manage as SJS/TEN/EM major, DRESS, or HSR as applicable (see below).</li> </ul> <p><b>Rash in Patients Receiving NVP:</b></p> <ul style="list-style-type: none"> <li>• Given the elevated risk of HSR, measure hepatic transaminases.</li> <li>• If hepatic transaminases are elevated, NVP <b>should be discontinued and not restarted</b> (see the HSR section below).</li> </ul>
<b>SJS/TEN/EM Major</b>	Many ARV drugs, especially NNRTIs (see the Estimated Frequency column)	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• First few days to weeks after starting new ARV drug(s)</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• 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.</li> </ul>	<p><b>Infrequent:</b></p> <ul style="list-style-type: none"> <li>• NVP (0.3%)</li> <li>• EFV (0.1%)</li> <li>• ETR (&lt;0.1%)</li> </ul> <p><b>Case Reports:</b></p> <ul style="list-style-type: none"> <li>• ABC</li> <li>• ATV</li> <li>• DRV</li> <li>• LPV/r</li> <li>• RAL</li> <li>• ZDV</li> </ul>	<p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>• Female sex</li> <li>• Patients who are black, Asian, or Hispanic are at higher risk.</li> </ul>	<p><b>When Starting NVP or Restarting NVP After Interruptions of &gt;14 Days:</b></p> <ul style="list-style-type: none"> <li>• Utilize once-daily lead-in dosing.<sup>a</sup> This may not be necessary in children aged &lt;2 years.<sup>b</sup></li> <li>• Counsel families to report symptoms as soon as they appear.</li> </ul>	<p>Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX).</p> <p>Provide intensive supportive care, including IV hydration, aggressive wound care, eye care, labial adhesion preventative care, pain management, and antipyretics. Parenteral nutrition and antibiotics may also be necessary.</p> <p>Corticosteroids and/or IVIG are sometimes used, but the use of these interventions is controversial.</p> <p><b>Do not reintroduce</b> the offending medication.</p> <p>In cases where a patient experiences SJS/TEN/EM major while taking an NNRTI, many experts would avoid using other NNRTIs when restarting ART.</p>

**Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated April 14, 2020; last reviewed April 14, 2020) (2 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>DRESS</b>	DRV, DTG, EFV, ETR, NVP, RAL, RPV	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• 1–8 weeks after starting new ARV drug(s)</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Fever</li> <li>• Lymphadenopathy</li> <li>• Facial swelling</li> <li>• Morbilliform to polymorphous rash</li> <li>• Peripheral eosinophilia</li> <li>• Atypical circulating lymphocytes</li> <li>• Internal organ involvement (particularly the liver and/or kidneys)</li> </ul>	Rare	Unknown	Obtain a CBC and AST, ALT, and creatinine levels from patients who present with suggestive symptoms.	<p>Discontinue all ARV drugs and other possible causative agents (e.g., TMP-SMX).</p> <p>The role of systemic steroids in treatment is unclear; consultation with a specialist is recommended.</p> <p>Provide supportive care for endorgan disease.</p> <p><b>Do not reintroduce</b> the offending medication.</p>
<p><b>HSR</b></p> <p>With or without skin involvement and excluding SJS/TEN</p>	ABC	<p><b>Onset</b></p> <p><i>With First Use:</i></p> <ul style="list-style-type: none"> <li>• Within first 6 weeks of initiating ABC</li> </ul> <p><i>With Reintroduction:</i></p> <ul style="list-style-type: none"> <li>• Within hours of initiating ABC</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, and respiratory symptoms (e.g., dyspnea).</li> <li>• With continuation of ABC, symptoms may progress to hypotension and vascular collapse. With rechallenge, symptoms can mimic anaphylaxis.</li> </ul>	<1% to 9% (varies by ethnicity)	<p>HLAB*5701 (HSR is very uncommon in people who are HLAB*5701 negative).</p> <p>The risk of HSR is higher in patients who are white than in patients who are black or East Asian.</p>	<p>Screen for HLAB*5701. <b>ABC should not be prescribed if HLAB*5701 is present.</b> The medical record should clearly indicate that ABC is <b>contraindicated</b> in these patients.</p> <p>When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.</p>	<p>Discontinue all ARV drugs and investigate other causes of the symptoms (e.g., a concurrent viral illness).</p> <p>Provide symptomatic treatment.</p> <p>Most symptoms resolve within 48 hours after discontinuing ABC.</p> <p><b>Do not rechallenge</b> with ABC even if the patient is HLAB*5701 negative.</p>

**Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated April 14, 2020; last reviewed April 14, 2020) (3 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR, continued	NVP	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>Occurs most frequently in the first few weeks of therapy, but can occur through 18 weeks</li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Flulike symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy</li> </ul>	Occurs in 4% of patients on average, with a range of 2.5% to 11%	<p><b>Adults:</b></p> <ul style="list-style-type: none"> <li>ARV-naïve with a higher CD4 count (&gt;250 cells/mm<sup>3</sup> in women; &gt;400 cells/mm<sup>3</sup> in men)</li> <li>Female sex (risk is 3-fold higher in females than in males).</li> </ul> <p><b>Children:</b></p> <ul style="list-style-type: none"> <li>NVP hepatotoxicity and HSR are less common in prepubertal children than in adults, and both are uncommon in infants.</li> <li>High CD4 percentage is associated with an increased risk of NVP toxicity. In the PREDICT study, the risk of NVP toxicity (rash, hepatotoxicity, and hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages &lt;15%.</li> </ul>	<p><b>When Starting NVP or Restarting NVP After Interruptions of &gt;14 Days:</b></p> <ul style="list-style-type: none"> <li>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.<sup>a</sup> This may not be necessary in children aged &lt;2 years.<sup>b</sup></li> <li>Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.</li> <li>Obtain AST and ALT levels in patients with rash.</li> <li>Obtain AST and ALT levels at baseline, before dose escalation, 2 weeks after dose escalation, and thereafter at 3-month intervals.</li> <li>Avoid NVP use in women with CD4 counts &gt;250 cells/mm<sup>3</sup> and in men with CD4 counts &gt;400 cells/mm<sup>3</sup>, unless benefits outweigh risks.</li> <li>Do not use NVP as PEP outside of the neonatal period.</li> </ul>	<p>Discontinue all ARV drugs.</p> <p>Consider other causes for hepatitis and discontinue all hepatotoxic medications.</p> <p>Provide supportive care as indicated and monitor the patient closely.</p> <p><b>Do not reintroduce NVP.</b> It is unclear whether it is safe to use other NNRTIs after a patient experiences symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.</p>

**Table 15k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated April 14, 2020; last reviewed April 14, 2020) (4 of 4)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR, continued	ETR	<b>Onset:</b> <ul style="list-style-type: none"> <li>Any time during therapy</li> </ul> <b>Presentation:</b> <ul style="list-style-type: none"> <li>Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.</li> </ul>	Rare	Unknown	Evaluate for hypersensitivity if the patient is symptomatic.	Discontinue all ARV drugs. Rechallenge with ETR <b>is not recommended</b> .
	MVC	Rash preceding hepatotoxicity	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	Discontinue all ARV drugs. Rechallenge with MVC <b>is not recommended</b> .
	DTG	Rash with hepatic dysfunction	Rare	Unknown	Obtain AST and ALT levels from patients with rash or other symptoms of hypersensitivity.	Discontinue all ARV drugs. Rechallenge with DTG is <b>contraindicated</b> .

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

<sup>b</sup> Lead-in dosing **is not recommended** when using NVP for either **presumptive** or definitive HIV therapy in newborns with perinatal HIV exposure or perinatal HIV infection. See the [Nevirapine](#) section of the Drug Appendix and [Table 12](#).

**Key:** ABC = abacavir; ALT = alanine transaminase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP = cytochrome P; 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

## References

- Borras-Blasco J, Navarro-Ruiz A, Borras C, Castera E. Adverse cutaneous reactions associated with the newest antiretroviral drugs in patients with human immunodeficiency virus infection. *J Antimicrob Chemother.* 2008;62(5):879-888. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18653488>.
- Davis CM, Shearer WT. Diagnosis and management of HIV drug hypersensitivity. *J Allergy Clin Immunol.* 2008;121(4):826-832 e825. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18190954>.

3. Kea C, Puthanakit T, Apornpong T, et al. Incidence and risk factors for nevirapine related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. Presented at: 6th International AIDS Society Conference on HIV Pathogenesis and Treatment and Prevention. 2011. Rome, Italy.
4. Mallal S, Phillips E, Carosi G, et al. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18256392>.
5. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clin Pharmacokinet*. 2000;39(4):281-293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11069214>.
6. Puthanakit T, Bunupuradah T, Kosalaraksa P, et al. Prevalence of human leukocyte antigen-B\*5701 among HIV-infected children in Thailand and Cambodia: implications for abacavir use. *Pediatr Infect Dis J*. 2013;32(3):252-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22986704>.
7. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr*. 2003;34 Suppl 1(Suppl 1):S21-33. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14562855>.
8. Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS*. 2013;27(9):1403-1412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23343913>.
9. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology*. 2003;206(4):353-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12771485>.
10. Trottier B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. *J Acquir Immune Defic Syndr*. 2005;40(4):413-421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16280695>.
11. Vitezica ZG, Milpied B, Lonjou C, et al. HLA-DRB1\*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS*. 2008;22(4):540-541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18301070>.
12. Yuan J, Guo S, Hall D, et al. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. *AIDS*. 2011;25(10):1271-1280. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21505298>.
13. Dziuban EJ, Hughey AB, Stewart DA, et al. Stevens-Johnson syndrome and HIV in children in Swaziland. *Pediatr Infect Dis J*. 2013;32(12):1354-1358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23743542>.
14. Rutstein RM, Samson P, Fenton T, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the pediatric AIDS clinical trials group protocol 1020A. *Pediatr Infect Dis J*. 2015;34:162-167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25232777>.
15. Perry ME, Almaani N, Desai N, Larbalestier N, Fox J, Chilton D. Raltegravir-induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome—implications for clinical practice and patient safety. *Int J STD AIDS*. 2013;24(8):639-642. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23970584>.
16. Bourezane Y, Salard D, Hoen B, Vandell S, Drobacheff C, Laurent R. DRESS (drug rash with eosinophilia and systemic symptoms) syndrome associated with nevirapine therapy. *Clin Infect Dis*. 1998;27(5):1321-1322. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9827291>.
17. Ripamonti D, Benatti SV, Di Filippo E, Ravasio V, Rizzi M. Drug reaction with eosinophilia and systemic symptoms associated with raltegravir use: case report and review of the literature. *AIDS*. 2014;28(7):1077-1079. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24685746>.
18. Noguera-Morel L, Hernandez-Martin A, Torrelo A. Cutaneous drug reactions in the pediatric population. *Pediatr Clin North Am*. 2014;61(2):403-426. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24685746>.

<http://www.ncbi.nlm.nih.gov/pubmed/24636653>.

19. Bossi P, Colin D, Bricaire F, Caumes E. Hypersensitivity syndrome associated with efavirenz therapy. *Clin Infect Dis*. 2000;30(1):227-228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10619772>.
20. Prasertvit P, Chareonyingwattana A, Wattanakrai P. Nevirapine patch testing in Thai human immunodeficiency virus infected patients with nevirapine drug hypersensitivity. *Contact Dermatitis*. 2017;77(6):379-384. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28782122>.
21. Shah R, Nabiswa H, Okinda N, Revathi G, Hawken M, Nelson M. Prevalence of HLA-B\*5701 in a Kenyan population with HIV infection. *J Infect*. 2018;76(2):212-214. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28919349>.
22. Martin C, Payen MC, De Wit S. Dolutegravir as a trigger for DRESS syndrome? *Int J STD AIDS*. 2018;29(10):1036-1038. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29621952>.
23. Fillekes Q, Mulenga V, Kabamba D, et al. Is nevirapine dose escalation appropriate in young, african, HIV-infected children? *AIDS*. 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23595153>.
24. Nishijima T, Gatanaga H, Teruya K, et al. Skin rash induced by ritonavir-boosted darunavir is common, but generally tolerable in an observational setting. *J Infect Chemother*. 2014;20(4):285-287. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24507978>.
25. Tudor-Williams G, Cahn P, Chokephaibulkit K, et al. Etravirine in treatment-experienced, HIV-1-infected children and adolescents: 48-week safety, efficacy and resistance analysis of the phase II PIANO study. *HIV Med*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24589294>.
26. Nachman S, Alvero C, Tepler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a phase 1/2 open label, non-randomised, multicentre trial. *Lancet HIV*. 2018;5(12):e715-e722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30527329>.
27. Mounzer K, Hsu R, Fusco JS, et al. HLA-B\*57:01 screening and hypersensitivity reaction to abacavir between 1999 and 2016 in the OPERA((R)) observational database: a cohort study. *AIDS Res Ther*. 2019;16(1):1. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30651100>.

# Management of Children Receiving Antiretroviral Therapy (Last updated April 14, 2020; last reviewed April 14, 2020)

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:

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

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

Panel's Recommendations
<ul style="list-style-type: none"><li>• 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 (<b>AII</b>).</li><li>• 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, <b>drug cost, the patient's insurance coverage</b>, and the patient's ability to tolerate the new drug regimen (<b>AIII</b>). Archived drug resistance can limit the antiviral activity of a new drug regimen.</li><li>• 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 (<b>BIII</b>).</li></ul>
<p><b>Rating of Recommendations:</b> A = Strong; B = Moderate; C = Optional</p> <p><b>Rating of Evidence:</b> I = One or more randomized trials in children<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> 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<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion</p> <p><sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents</p>

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. New ARV drug options may become available as children grow and learn to swallow pills, and as new drugs, drug formulations, and data become available. Even in cases where patients have achieved sustained virologic suppression (i.e., suppression for 6–12 months) on their current regimen, clinicians should consider switching patients to new ARV regimens 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.<sup>1</sup> These changes often enhance adherence and improve quality of life.<sup>2</sup>

### Treatment Simplification

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

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 [ABC], nevirapine [NVP]) maintain virologic suppression when they switch from twice-daily regimens to once-daily regimens (see the [Abacavir](#) and [Nevirapine](#) sections and fixed-dose combinations [FDCs] in Appendix A, [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**.<sup>3-7</sup>

### ***Treatment Optimization***

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. Treatment optimization may include improving the potency of the regimen, improving a child's growth or other health outcomes through reduced drug side effects and/or better treated HIV, or maximizing palatability. Despite concerns about drug class resistance, the results of the NEVEREST 2 study demonstrated that young children (i.e., those aged <2 years) with virologic suppression who switched from a LPV/r-based regimen to a NVP-based regimen maintained virologic suppression as well as those who continued taking LPV/r, provided that they had good adherence and no baseline resistance to NVP.<sup>8,9</sup> In the NEVEREST 3 study, children aged ≥3 years who had a history of exposure to NVP and who achieved virologic suppression on a LPV/r-based regimen maintained virologic suppression when switched from LPV/r to an efavirenz (EFV)-based regimen.<sup>10-12</sup> Similarly, in the NEVEREST 2 study, children who switched to a NVP-based regimen showed better immune and growth responses than those who stayed on a LPV/r-based regimen.<sup>8</sup> 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 [DTG]) would likely be effective, but these substitutions have not been directly studied in children.

### ***Toxicity Management***

Several studies of small cohorts of children have demonstrated sustained virologic suppression and reassuring safety outcomes when drugs that have greater long-term toxicity risks are replaced with drugs that are thought to have lower toxicity risks (e.g., replacing stavudine with tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine, or ABC; replacing PIs with non-nucleoside reverse transcriptase inhibitors), including improved lipid profiles.<sup>13-17</sup> **Additionally, studies in adults have shown improvement in tolerability, lipid profiles, and insulin sensitivity in patients who switched from PIs to INSTIs,<sup>18-22</sup> and adults who switched from EFV to an INSTI have shown improvement in neuropsychiatric symptoms. However, the use of INSTIs has been associated with weight gain in adults; this association has not yet been evaluated in children.<sup>23</sup>**

### ***Regimens That Are Not Recommended for Use in Children***

Two-drug regimens and monotherapy PI regimens (darunavir/ritonavir, LPV/r, atazanavir/ritonavir)<sup>24,25</sup> or monotherapy regimens of DTG<sup>26,27</sup> 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.<sup>25,28-31</sup>

The FDC tablet that contains DTG/rilpivirine (RPV), a nucleoside-sparing, dual-therapy regimen that is marked as Juluca, is 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 DTG/RPV or to stay on their original regimens. Results from these trials showed similar rates of virologic suppression in both groups (noninferiority) through 48 weeks.<sup>32</sup> 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 the use of 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 drug 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. **Among treatment-naïve youth in the United States aged 13 to 24 years, there is some evidence that single-tablet regimens (STRs) improve the odds of viral suppression.<sup>33</sup> While these data have not been replicated in treatment-experienced adolescents, clinicians should still consider using STRs in children and youth with sustained suppression, as these regimens reduce pill burden and dosing frequency.** 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.<sup>34-38</sup> 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 2–4 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)

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, such as drug cost and the patient’s insurance coverage.** 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.

<b>Current ARV Drug(s)</b>	<b>Age, Weight, and SMR Requirements</b>	<b>Potential ARV Drug Switch</b>	<b>Comment</b>
<b>NRTIs</b>			
<b>ABC Twice Daily</b>	Aged ≥1 year	ABC once daily	See the <a href="#">Abacavir<sup>a</sup></a> section.
<b>3TC Twice Daily</b>	Aged ≥3 years	3TC once daily	See the <a href="#">Lamivudine</a> section.
	<b>Any age (starting at full-term birth)</b> <b>Any weight</b>	<b>FTC once daily</b>	See the <a href="#">Emtricitabine</a> section.
<b>ZDV, ddl, or d4T<sup>b</sup></b>  <b>Note: ddl and d4T should be replaced as soon as possible due to concerns about toxicity.</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 as an oral powder and low-strength tablets alone or in combination with FTC.
	Aged ≥2 years Weighing ≥25 kg	TAF <sup>c</sup>	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.
<b>NNRTIs</b>			
<b>NVP or EFV</b>	Any age (starting at full-term birth) Weighing ≥2 kg	RAL <sup>d</sup>	RAL has a potentially greater barrier to resistance than NVP. Both are dosed twice daily in children.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	ATV/r has a potentially greater barrier to resistance; however, taking ATV/r may be difficult for some patients, as ATV oral powder must be mixed with food or a beverage before administration, and the palatability of the RTV oral solution is poor.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r has a potentially greater barrier to resistance. DRV/r is administered twice daily to patients aged <12 years, but may be administered once daily in children aged ≥12 years who do not have any DRV resistance mutations.

**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
<b>NNRTIs, continued</b>			
NVP or EFV, continued	Weighing ≥25 kg	BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
	Weighing ≥25 kg	EVG as Genvoya	EVG is available as a component of the FDC tablet EVG/c/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥20 kg	DTG	DTG is available as a smaller, single-drug tablet or as an FDC tablet, both of which can be dosed once daily if no INSTI resistance mutations have been previously detected. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. DTG is available as a component of the FDC tablet ABC/DTG/3TC (Triumeq), which is a complete ARV regimen that can be given to children weighing ≥25 kg. Higher barrier to resistance, which makes it a good choice for patients who have poor adherence. May improve lipid levels. See the <a href="#">Dolutegravir</a> section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents. <sup>9</sup>
	Aged ≥12 years Weighing ≥35 kg	RPV	Lower incidence of adverse lipid effects.
<b>PIs</b>			
LPV/r Twice Daily	Any age (starting at full-term birth) Weighing ≥2 kg	RAL <sup>d</sup>	Better palatability. RAL HD can only be given once daily in those weighing ≥40 kg. Unlike LPV/r, the use of RAL is not restricted to infants with a corrected gestational age of ≥42 weeks and a postnatal age of ≥14 days. RAL granules may be difficult to dose for some caregivers.
	Aged ≥3 years Weighing ≥10 kg	EFV	Once-daily dosing. Better palatability. Lower incidence of adverse lipid effects. See the <a href="#">Efavirenz</a> section for concerns about EFV dosing for children aged <3 years.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	Once-daily dosing. ATV/r may have a lower incidence of adverse lipid effects; however, taking ATV/r may be difficult for some patients, as ATV oral powder must be mixed with food or a beverage before administration, and the palatability of the RTV oral solution is poor.
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r may have a lower incidence of adverse lipid effects. DRV/r is administered twice daily to patients aged <12 years, but 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 tablet EVG/c/FTC/TAF (Genvoya), which is a complete ARV regimen that must be taken with food.
	Weighing ≥20 kg	DTG	Once-daily dosing if no INSTI resistance mutations have been previously detected. May be better tolerated, and can be given as an FDC tablet to children weighing ≥25 kg. DTG plus the weight-appropriate dose of FTC/TDF (Truvada) can be used in children weighing 20 kg to <25 kg. May improve lipid levels. See the <a href="#">Dolutegravir</a> section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents. <sup>9</sup>
	Aged ≥12 years Weighing ≥35 kg	RPV	May be better tolerated. Lower incidence of adverse lipid effects.
	Weighing ≥25 kg	BIC as Biktarvy	Once-daily dosing. BIC is available as a component of the FDC tablet BIC/FTC/TAF (Biktarvy), which is a complete ARV regimen that can be taken with or without food.
	<b>Other</b>		
Any Multi-Pill and/or Twice-Daily Regimen	Weighing ≥25 kg	EVG/c/FTC/TAF (Genvoya)	Once-daily dosing. Single pill. Alignment with adult regimens. Must be taken with food.
	Weighing ≥25 kg	FTC/TAF <sup>c</sup> (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 <a href="#">Dolutegravir</a> section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents. <sup>9</sup>

**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
<b>Other, continued</b>			
<b>Any Multi-Pill and/or Twice-Daily Regimen, continued</b>	Weighing ≥35 kg SMR 4 or 5	EVG/c/FTC/TDF (Stribild)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food. Renal and bone toxicity of TDF limit its use.
	Aged ≥12 years Weighing ≥35 kg	FTC/RPV/TAF (Odefsey)	Once-daily dosing. Single pill. Aligns a child's regimen with an efficacious regimen that is used in adults. Must be taken with food at a consistent time daily.
	Weighing ≥25 kg	BIC/FTC/TAF (Biktarvy)	Once-daily dosing. Single pill that can be taken with or without food.
	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. <b>Renal and bone toxicity of TDF limit its use.</b>
	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 <a href="#">Dolutegravir</a> section for information regarding use of DTG in female adolescents of childbearing potential and pregnant adolescents. <sup>e</sup>
	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. <b>Renal and bone toxicity of TDF as well as CNS toxicity of Efavirenz limit its use.</b>

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

<sup>b</sup> See [Archived Drugs](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#).

<sup>c</sup> 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.

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

<sup>e</sup> **Exposure to DTG around the time of conception has been associated with a small but significant increase in the risk of infant neural tube defects.** Additional information and specific recommendations about the use of DTG in adolescents and adults who are pregnant and those who are trying to conceive or who may become pregnant 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, Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D. Dolutegravir Counseling Guide for Health Care Providers](#)).

**Key:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; d4T = stavudine; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; Efavirenz = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; HD = high dose; HLA = human leukocyte antigen; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

## References

- Hsu AJ, Neptune A, Adams C, Hutton N, Agwu AL. Antiretroviral stewardship in a pediatric HIV clinic: development, implementation and improved clinical outcomes. *Pediatr Infect Dis J*. 2016;35(6):642-648. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26906161>.
- Maiese EM, Johnson PT, Bancroft T, Goolsby Hunter A, Wu AW. Quality of life of HIV-infected patients who switch antiretroviral medication due to side effects or other reasons. *Curr Med Res Opin*. 2016:1-8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27552553>.
- Foissac F, Blanche S, Dollfus C, et al. Population pharmacokinetics of atazanavir/ritonavir in HIV-1-infected children and adolescents. *Br J Clin Pharmacol*. 2011;72(6):940-947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21649692>.

4. Chokephaibulkit K, Prasitsuebsai W, Wittawatmongkol O, et al. Pharmacokinetics of darunavir/ritonavir in Asian HIV-1-infected children aged  $\geq 7$  years. *Antivir Ther.* 2012;17(7):1263-1269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22954687>.
5. Lyall H. Final results of Koncert: A randomized noninferiority trial of QD vs BD LPV/r dosing in children. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, Massachusetts.
6. Paediatric European Network for Treatment of AIDS. Once vs. twice-daily lopinavir/ritonavir in HIV-1-infected children. *AIDS.* 2015;29(18):2447-2457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26558544>.
7. Gondrie IPE, Bastiaans DET, Fraaij PLA, et al. Sustained viral suppression in HIV-infected children on once-daily lopinavir/ritonavir in clinical practice. *Pediatr Infect Dis J.* 2017;36(10):976-980. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28475554>.
8. Coovadia A, Abrams EJ, Strehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA.* 2010;304(10):1082-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823434>.
9. Kuhn L, Coovadia A, Strehlau R, et al. Switching children previously exposed to nevirapine to nevirapine-based treatment after initial suppression with a protease-inhibitor-based regimen: long-term follow-up of a randomised, open-label trial. *Lancet Infect Dis.* 2012;12(7):521-530. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22424722>.
10. Coovadia A, Abrams E, Strehlau R, et al. NEVEREST Study Team. Virologic efficacy of efavirenz maintenance therapy in nevirapine prophylaxis-exposed children. Abstract #73. Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, Massachusetts.
11. Coovadia A, Abrams EJ, Strehlau R, et al. Efavirenz-based antiretroviral therapy among nevirapine-exposed HIV-infected children in South Africa: a randomized clinical trial. *JAMA.* 2015;314(17):1808-1817. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26529159>.
12. Murnane PM, Strehlau R, Shiao S, et al. Switching to efavirenz versus remaining on ritonavir-boosted lopinavir in HIV-infected children exposed to nevirapine: long-term outcomes of a randomized trial. *Clin Infect Dis.* 2017;65(3):477-485. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28419200>.
13. Vigano A, Aldrovandi GM, Giacomet V, et al. Improvement in dyslipidaemia after switching stavudine to tenofovir and replacing protease inhibitors with efavirenz in HIV-infected children. *Antivir Ther.* 2005;10(8):917-924. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16430197>.
14. Fabiano V, Giacomet V, Vigano A, et al. Long-term body composition and metabolic changes in HIV-infected children switched from stavudine to tenofovir and from protease inhibitors to efavirenz. *Eur J Pediatr.* 2013;172(8):1089-1096. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23636286>.
15. Rosso R, Nasi M, Di Biagio A, et al. Effects of the change from stavudine to tenofovir in human immunodeficiency virus-infected children treated with highly active antiretroviral therapy: studies on mitochondrial toxicity and thymic function. *Pediatr Infect Dis J.* 2008;27(1):17-21. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18162932>.
16. Aupibul L, Puthanakit T, Sirisanthana T, Sirisanthana V. Haematological changes after switching from stavudine to zidovudine in HIV-infected children receiving highly active antiretroviral therapy. *HIV Med.* 2008;9(5):317-321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18331562>.
17. Gonzalez-Tome MI, Amador JT, Pena MJ, Gomez ML, Conejo PR, Fontelos PM. Outcome of protease inhibitor substitution with nevirapine in HIV-1 infected children. *BMC Infect Dis.* 2008;8:144. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18945352>.
18. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, Phase 3b, non-inferiority trial. *Lancet Infect Dis.* 2014;14(7):581-589. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24908551>.
19. Martinez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS.* 2010;24(11):1697-1707. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20467288>.
20. Curran A, Martinez E, Saumoy M, et al. Body composition changes after switching from protease inhibitors to raltegravir: SPIRAL-LIP substudy. *AIDS.* 2012;26(4):475-481. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22112606>.

21. Bagella P, Squillace N, Ricci E, et al. Lipid profile improvement in virologically suppressed HIV-1-infected patients switched to dolutegravir/abacavir/lamivudine: data from the SCOLTA project. *Infect Drug Resist.* 2019;12:1385-1391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31213857>.
22. Calza L, Colangeli V, Borderi M, et al. Improvement in insulin sensitivity and serum leptin concentration after the switch from a ritonavir-boosted PI to raltegravir or dolutegravir in non-diabetic HIV-infected patients. *J Antimicrob Chemother.* 2019;74(3):731-738. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30541118>.
23. Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis.* 2014;14(7):590-599. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24908550>.
24. Soriano V, Fernandez-Montero JV, Benitez-Gutierrez L, et al. Dual antiretroviral therapy for HIV infection. *Expert Opin Drug Saf.* 2017;16(8):923-932. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28621159>.
25. Arribas JR, Girard PM, Paton N, et al. Efficacy of protease inhibitor monotherapy vs. triple therapy: meta-analysis of data from 2303 patients in 13 randomized trials. *HIV Med.* 2016;17(5):358-367. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26709605>.
26. Brenner BG, Thomas R, Blanco JL, et al. Development of a G118R mutation in HIV-1 integrase following a switch to dolutegravir monotherapy leading to cross-resistance to integrase inhibitors. *J Antimicrob Chemother.* 2016;71(7):1948-1953. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27029845>.
27. Wiiting I, Rokx C, Wit F, et al. Integrase inhibitors are an independent risk factor for IRIS: an ATHENA cohort study. Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
28. Rokx C, Schurink CA, Boucher CA, Rijnders BJ. Dolutegravir as maintenance monotherapy: first experiences in HIV-1 patients. *J Antimicrob Chemother.* 2016;71(6):1632-1636. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26888910>.
29. Pinnetti C, Lorenzini P, Cozzi-Lepri A, et al. Randomized trial of DRV/r or LPV/r QD monotherapy vs maintaining a PI/r-based antiretroviral regimen in persons with suppressed HIV replication. *J Int AIDS Soc.* 2014;17(4 Suppl 3):19809. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25397553>.
30. Santos JR, Llibre JM, Bravo I, et al. Short communication: efficacy and safety of treatment simplification to lopinavir/ritonavir or darunavir/ritonavir monotherapy: a randomized clinical trial. *AIDS Res Hum Retroviruses.* 2016;32(5):452-455. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26781004>.
31. Kosalaraksa P, Ananworanich J, Puthanakit T, et al. Long-term lopinavir/ritonavir monotherapy in HIV-infected children. *Pediatr Infect Dis J.* 2013;32(4):350-353. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23190774>.
32. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-ritonavir for the maintenance of virological suppression in adults with HIV-1: Phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet.* 2018;391(10123):839-849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29310899>.
33. Griffith DC, Farmer C, Gebo KA, et al. Uptake and virological outcomes of single- versus multi-tablet antiretroviral regimens among treatment-naive youth in the HIV research network. *HIV Med.* 2019;20(2):169-174. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30561888>.
34. Agwu AL, Fairlie L. Antiretroviral treatment, management challenges and outcomes in perinatally HIV-infected adolescents. *J Int AIDS Soc.* 2013;16:18579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23782477>.
35. Wensing AM, Calvez V, Gunthard HF, et al. 2015 Update of the drug resistance mutations in HIV-1. *Top Antivir Med.* 2015;23(4):132-141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26713503>.
36. Dehority W, Deville JG, Lujan-Zilbermann J, Spector SA, Viani RM. Effect of HIV genotypic drug resistance testing on the management and clinical course of HIV-infected children and adolescents. *Int J STD AIDS.* 2013;24(7):549-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23970770>.
37. Tobin NH, Learn GH, Holte SE, et al. Evidence that low-level viremia during effective highly active antiretroviral therapy result from two processes: expression of archival virus and replication of virus. *J Virol.* 2005;79(15):9625-9634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16014925>.
38. Kuritzkes DR. Preventing and managing antiretroviral drug resistance. *AIDS Patient Care STDS.* 2004;18(5):259-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15186710>.

## Recognizing and Managing Antiretroviral Treatment Failure (Last updated April 14, 2020; last reviewed April 14, 2020)

### 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 (**All**).
- Perform ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen (**AI\***) (see [Drug-Resistance Testing](#) in the Adult and Adolescent Antiretroviral Guidelines for more information).
- ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results (**AI\***).
- The new regimen should include at least two, but preferably three, fully active ARV medications; the assessment of anticipated ARV activity should be based on treatment history and past resistance test results (**All\***).
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, which is defined as a plasma viral load that is below the limits of detection as measured by highly sensitive assays with lower limits of quantification of 20 copies/mL to 75 copies/mL (**AI\***).
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent the development of additional drug resistance that could further limit future ARV drug options (**All**).
- 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 (OIs) (excluding immune reconstitution inflammatory syndrome [IRIS]) and/or other clinical evidence of HIV disease progression during therapy. Almost all antiretroviral (ARV) management decisions for treatment failure are based on addressing virologic failure.

### Virologic Failure

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

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

There is controversy regarding the clinical implications of HIV RNA levels that are between the lower level of detection and <200 copies/mL in patients on antiretroviral therapy (ART). 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.<sup>4-6</sup> 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.<sup>7-10</sup> “Blips”—defined as isolated episodes of a detectable but low level of plasma viral load (i.e., <500 copies/mL) that are followed by a return to viral suppression—are common and not generally reflective of short-term virologic failure, though they may indicate an increased risk of virologic failure after 12 months to 24 months.<sup>11-13</sup> However, repeated or persistent plasma viral loads that are ≥200 copies/mL (especially viral loads that are >500 copies/mL) in patients who have achieved virologic suppression usually indicates virologic failure.<sup>6,13-15</sup>

### **Poor Immunologic Response Despite Virologic Suppression**

Poor immunologic response despite virologic suppression is uncommon in children.<sup>16</sup> Patients with baseline severe immunosuppression (i.e., a CD4 T lymphocyte [CD4] cell count >500 cells/mm<sup>3</sup>) often take more than 1 year to achieve immune recovery, even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur.

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

Patients who have very low baseline CD4 values before initiating ART are at higher risk of an impaired CD4 response to ART and, based on data from adult studies, may be at higher risk of death and AIDS-defining illnesses despite virologic suppression.<sup>17-19</sup> In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 348 children (37%) had CD4 counts <500 cells/mm<sup>3</sup> at ART initiation, including 92 (9.9%) who had CD4 counts <200 cells/mm<sup>3</sup>. After 1 year of virologic suppression, only seven children (1% of the cohort) failed to reach a CD4 count ≥200 cells/mm<sup>3</sup>, and 86% of children had CD4 counts >500 cells/mm<sup>3</sup>. AIDS-defining events were uncommon overall (occurring in 1% of participants), but they occurred both in children who did achieve improved CD4 counts and those who did not.<sup>16</sup>

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C virus, tuberculosis [TB], malnutrition, Sjogren’s syndrome, sarcoidosis, syphilis, **cirrhosis**, acute viral infections) are independently associated with low CD4 values.<sup>20</sup>

In summary, poor immunologic response to treatment can occur. Management consists of confirming that CD4 values and viral load measurements are accurate, avoiding the use of drugs that are associated with low CD4 values, and treating other conditions that could impair CD4 recovery. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV 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. At times, after initiation of ART, patients will suffer a clinical deterioration due to paradoxical worsening of a known OI, or unmasking of a previously undiagnosed OI, due to a profound immune response (IRIS) related to successful viral suppression. This does not represent ART treatment failure, and does not generally require discontinuation of, or a change in ART. IRIS does not mean that ART has failed, and it does not generally

require discontinuation of ART.<sup>21,22</sup> 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.<sup>23</sup> Such cases do not represent ART failure, and these children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should also be evaluated to rule out (and, when indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary TB, malnutrition, and malignancy.

Occasionally, however, children will develop new HIV-related OIs (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis that occurs more than 6 months after achieving markedly improved CD4 values and virologic suppression) that are not related to IRIS, pre-existing organ damage, or another cause.<sup>16</sup> Although such cases are rare, they may represent ART clinical failure, and improvement in CD4 values may not necessarily normalize immunologic function. In children who have signs of new or progressive abnormal neurodevelopment, some experts change the ARV regimen, aiming to include agents that are known to achieve higher concentrations in the central nervous system; however, the data regarding the effectiveness of this strategy are inconclusive.<sup>24,25</sup>

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

<b>Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression</b>
<p><b>Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:</b></p> <ul style="list-style-type: none"> <li>• Lab error (in CD4 value or viral load measurement)</li> <li>• Misinterpretation of normal, age-related CD4 count decline (i.e., the immunologic response is not actually poor)</li> <li>• Low pretreatment CD4 count or percentage</li> <li>• AEs that are associated with the use of certain drugs (e.g., ZDV, TMP-SMX, systemic corticosteroids)</li> <li>• Use of systemic corticosteroids or chemotherapeutic agents</li> <li>• Conditions that can cause low CD4 values (e.g., HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis)</li> </ul> <p><b>Poor Immunologic and Clinical Responses Despite Virologic Suppression:</b></p> <ul style="list-style-type: none"> <li>• Lab error</li> <li>• Falsely low viral load result for an HIV strain/type that is not detected by viral load assay (i.e., HIV-1 non-M groups, HIV-1 non-B subtypes, HIV-2)</li> <li>• Persistent immunodeficiency that occurs soon after initiating ART but before ART-related reconstitution</li> <li>• Primary protein-calorie malnutrition</li> <li>• Untreated TB</li> <li>• Malignancy</li> </ul>
<b>Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses</b>
<ul style="list-style-type: none"> <li>• IRIS</li> <li>• A previously unrecognized, pre-existing infection or condition (e.g., TB, malignancy)</li> <li>• Malnutrition</li> <li>• Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy, <b>worsening neurodevelopmental delay</b>), lungs (e.g., bronchiectasis), cardiac (i.e., cardiomyopathy), renal (i.e., HIV-related kidney disease)</li> <li>• A new clinical event due to a non-HIV illness or condition</li> <li>• A new, otherwise unexplained HIV-related clinical event (e.g., treatment failure)</li> </ul>

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

### ***Management of Virologic Failure***

The approach to managing and subsequently treating virologic failure will differ depending on the etiology of the problem. When assessing a child with suspected virologic failure, clinicians should evaluate therapy adherence and medication intolerance, confirm that the prescribed dosing is correct (and understood by the

child and/or caregiver) for all medications in the regimen, consider possible pharmacokinetic (PK) interactions that might lead to low drug levels, and test for possible drug resistance (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). 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 ARV regimen. Please see [Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV](#) for guidance on assessing adherence and strategies for improving adherence.

### **Virologic Failure with No Antiretroviral Drug Resistance Identified**

Persistent viremia in the absence of detectable viral resistance to current medications is usually a result of nonadherence, but it is important to 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 discontinuing 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](#)). In this situation, resistance can be identified by restarting the prior medications while emphasizing adherence and repeating resistance testing in 4 weeks if plasma virus remains detectable. If the HIV plasma viral load becomes undetectable, then nonadherence was likely the original cause of virologic failure.

Virologic failure of boosted protease inhibitor (PI)-based regimens is frequently associated with no detected major PI resistance mutations. Virologic suppression may be achieved by continuing the PI-based regimen, implementing adherence-improvement measures, **and addressing any PI-related side effects**.<sup>26,27</sup>

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

### **Virologic Treatment Failure with Antiretroviral Drug Resistance Identified**

After deciding that a change in therapy is necessary, a clinician should attempt to identify at least two, but preferably three, fully active ARV agents from at least two different drug classes to use in a patient's new regimen. The clinician should consider all of the patient's past and recent drug-resistance test results, the patient's prior exposure to ARV drugs, whether the patient is likely to adhere to the regimen, and whether the patient finds a particular regimen acceptable.<sup>28-32</sup> This process often requires using agents from one or more drug classes that are new to the patient. However, clinicians should be aware that drug-resistance mutations can confer cross-resistance within a drug class, so a drug that is new to the patient may still have diminished antiviral potency. Substituting or adding a single drug to a failing regimen **is not recommended**, because this is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance.

The process of switching a patient to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient and the patient's caregivers. This discussion should be appropriate for the patient's age and stage of development. Clinicians should be aware that some medications have conflicting food requirements of and concomitant medication restrictions that 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.<sup>33</sup>

### ***Therapeutic Options to Achieve Complete Virologic Suppression After Virologic Failure***

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

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

Data from adult and pediatric studies support the efficacy of regimen that contains a boosted PI plus two nucleoside reverse transcriptase inhibitors (NRTIs) for those who experience treatment failure on an initial NNRTI-based regimen.<sup>34</sup> Studies of adults have found that a regimen that contains both a boosted PI and raltegravir (RAL) produces similar outcomes to a regimen that contains a boosted PI and two NRTIs.<sup>34,35</sup>

**A clinical trial in adults who had experienced treatment failure on an initial NNRTI-based regimen reported that dolutegravir (DTG) had better efficacy and a better safety profile than lopinavir/ritonavir (LPV/r) when these drugs were used in second-line regimens that included at least one active NRTI.<sup>36</sup>** Pediatric and adolescent data support the use of two NRTIs plus an integrase strand transfer inhibitor (INSTI) following the failure of an NNRTI-based regimen.<sup>37,38</sup>

However, caution should be exercised when considering the use of regimens that include first-generation INSTIs with a lower barrier to resistance (e.g., RAL), because children who experience treatment failure on NNRTI-based regimens often have substantial NRTI resistance.<sup>39</sup>

Resistance to the NNRTI nevirapine (NVP) results in cross-resistance to the NNRTI efavirenz (EFV), and vice versa. The NNRTIs etravirine (ETR) and rilpivirine (RPV) can retain activity against NVP-resistant virus or EFV-resistant virus in the absence of certain key NNRTI mutations (see below), but ETR has generally been tested only in regimens that also contain a boosted PI.<sup>28,40</sup>

If a child experiences virologic failure on an initial PI-based regimen, there are often limited resistance mutations detected, indicating that poor adherence/tolerance of the regimen may be the cause of poor viral control.<sup>39,41</sup> In these cases, an alternative PI that might be 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.<sup>42-44</sup> Darunavir/ritonavir-based therapy has also been used.<sup>45,46</sup> Based on more limited data, switching to an INSTI-based regimen can be effective.<sup>37,47</sup> **When making the switch from a failing PI-based regimen to an INSTI-based regimen, preference might be given to the second-generation INSTIs DTG or bictegravir (BIC), as these drugs have a higher barrier to resistance than the first-generation INSTIs RAL and elvitegravir.<sup>48</sup>**

**The availability of newer drugs within existing drug classes and the introduction of new classes of drugs** increase the likelihood of finding three active drugs, even for children with extensive drug resistance (see Table 18). As previously discussed, INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI-based regimens or PI-based regimens.<sup>37,49</sup> RAL is the INSTI that has been studied and used most often in children, but both DTG and BIC are appealing for their once-daily administration, small pill size, and higher barrier to development of drug resistance; they also retain ARV activity in patients who have experienced treatment failure on RAL-based therapy (see the [Dolutegravir](#) and [Bictegravir](#) sections for the latest age/weight indications). However, **use of DTG around the time of conception has been associated with a small, but significant, increase in the risk of infant neural tube defects** (see the [Dolutegravir](#) section). Additional information and specific recommendations about the use of DTG in women and adolescents of childbearing potential and in those who are pregnant **or who are trying to conceive** 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, Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D. Dolutegravir Counseling Guide for Health Care Providers](#)).

Maraviroc, a CCR5 antagonist, provides a new drug class, but many ART-experienced children already harbor CXCR4-tropic virus, which precludes its use.<sup>50</sup> Regimens that include an INSTI and a potent, boosted PI with or without ETR have been effective during small studies of extensively ART-experienced patients with multiclass drug resistance.<sup>51-54</sup> It is important to review individual drug profiles for information about drug interactions and dose adjustments when devising a regimen for children with multiclass drug resistance. [Appendix A: Pediatric](#)

[Antiretroviral Drug Information](#) provides detailed information on drug formulations, pediatric and adult doses, and toxicity, as well as discussions of the available data on the use of ARV drugs in children.

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

Some studies in adults have suggested that lamuvidine (3TC) can still contribute to suppression of HIV replication in patients with 3TC resistance mutations. Continuation of 3TC can also maintain a 3TC mutation (184V) that can partially reverse the effects of other mutations that confer resistance to zidovudine and tenofovir disoproxil fumarate.<sup>55-57</sup>

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 (T-20) is approved by the Food and Drug Administration (FDA) for use in ART-experienced children aged  $\geq 6$  years, but it must be administered by subcutaneous injection twice daily.<sup>58,59</sup> 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.<sup>60-62</sup> Regimens that contain more than three drugs (up to three PIs and/or two NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug-drug interactions.<sup>63</sup> The availability of the PI darunavir for children aged  $\geq 3$  years, the newer NNRTIs ETR and RPV, and more recent classes of ARV drugs (e.g., INSTIs, CCR5 inhibitors) have lessened the need for T-20, 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.<sup>64</sup>

Studies have compared the use of NRTI-sparing and NRTI-containing regimens in adults with multidrug resistance who experienced virologic failure on a previous regimen. These studies have demonstrated no clear benefit of including NRTIs in the new regimen.<sup>65,66</sup> One of these studies reported higher mortality in adults who were randomized to receive a regimen that included NRTIs than in adults who were randomized to receive an NRTI-sparing regimen.<sup>66</sup> 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 [AIDSinfo 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.<sup>67</sup> 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.<sup>68</sup>

Off-label use of ARV agents may be necessary for children with HIV who have limited ARV drug options. In this circumstance, consulting a pediatric HIV specialist for advice about potential regimens, assistance with access to unpublished data from clinical trials or other limited off-label pediatric use, and referral to suitable clinical trials 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 risks. Specifically, providers must balance the inherent tension between the benefits of virologic suppression and the risks of continued viral replication with potential evolution of viral drug resistance in the setting of inadequate ARV drug exposure (e.g., nonadherence or a nonsuppressive, suboptimal regimen). Nonsuppressive regimens could decrease viral fitness and thus slow clinical and immunologic deterioration while a patient is either working on adherence or awaiting access to new agents that are expected to achieve sustained virologic suppression.<sup>69</sup> However, persistent viremia in the context of ARV drug pressure has the potential to generate additional resistance mutations that could further compromise agents in the same class that might otherwise have been active in subsequent regimens (e.g., continuing first-generation INSTIs or NNRTIs). Patients who continue to use nonsuppressive regimens should be followed more closely than those with stable virologic status, and the potential to successfully initiate a fully suppressive 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 with the M184V resistance mutation and documented nonadherence to continue their nonsuppressive, non-NNRTI-based regimen or to switch to a 3TC (or emtricitabine [FTC]) monotherapy holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 count (the primary outcome) over a 28-week period. Only patients in the 3TC/FTC arm experienced the primary outcome.<sup>70</sup>

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](#)).<sup>71,72</sup>

**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** (page 1 of 2)

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 when 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. 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.

Prior Regimen	New Regimen Options <sup>a</sup>
Two NRTIs plus an NNRTI	Two NRTIs plus a boosted PI Two NRTIs plus an INSTI <sup>b</sup>
Two NRTIs plus a PI	Two NRTIs plus an INSTI Two NRTIs plus a different boosted PI INSTI plus a different boosted PI with or without an NNRTI and with or without NRTI(s)
Two NRTIs plus an INSTI	Two NRTIs plus a boosted PI DTG <sup>a,b</sup> or BIC <sup>b</sup> (if not used in the prior regimen) with a boosted PI with or without one or two NRTIs. DTG must be given twice daily if a patient has certain documented INSTI mutations, or if there is concern about certain mutations (see the <a href="#">Dolutegravir</a> section).

**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 (page 2 of 2)**

Prior Regimen	New Regimen Options <sup>a</sup>
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	<p><b>If NRTIs Are Fully Active:</b></p> <ul style="list-style-type: none"> <li>• INSTI plus two NRTIs</li> </ul> <p><b>If NRTIs Are Not Fully Active:</b></p> <ul style="list-style-type: none"> <li>• INSTI plus two NRTIs with or without an RTV-boosted PI</li> </ul> <p><b>If There is Minimal NRTI Activity:</b></p> <ul style="list-style-type: none"> <li>• INSTI with or without an RTV-boosted PI with or without ETR or RPV with or without NRTI(s)</li> <li>• Consider adding T-20 and/or MVC if additional active drug(s) are needed.</li> </ul>

<sup>a</sup> Exposure to DTG around the time of conception has been associated with a small but significant increase in the risk of infant NTDs. Additional information and specific recommendations about the use of DTG in women and adolescents of childbearing potential and in those who are pregnant or who are trying to conceive 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, Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D. Dolutegravir Counseling Guide for Health Care Providers](#)).

<sup>b</sup> RAL has a low barrier to resistance and requires twice-daily dosing in children and adolescents; BIC and DTG have a higher barrier to resistance and only require once-daily dosing.

**Key:** 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; BIC = bictegravir; 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; NTD = neural tube defect; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

## References

1. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS*. 2008;22(2):249-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18097227>.
2. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised Phase 2/3 trial. *Lancet Infect Dis*. 2011;11(4):273-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21288774>.
3. Eshleman SH, Krogstad P, Jackson JB, et al. Analysis of human immunodeficiency virus type 1 drug resistance in children receiving nucleoside analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir (Pediatric AIDS Clinical Trials Group 377). *J Infect Dis*. 2001;183(12):1732-1738. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11372025>.
4. Ribaldo HJ, Lennox, J., Currier J. et al. Virologic failure endpoint definition in clinical trials: is using HIV-1 RNA threshold <200 copies/mL better than <50 copies/mL? an analysis of ACTG Studies. Abstract #580. Presented at: Conference on Retroviruses and Opportunistic Infections. 2009.
5. Antiretroviral Therapy Cohort Collaboration, Vandenhende MA, Ingle S, et al. Impact of low-level viremia on clinical and virological outcomes in treated HIV-1-infected patients. *AIDS*. 2015;29(3):373-383. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25686685>.
6. Boillat-Blanco N, Darling KE, Schoni-Affolter F, et al. Virological outcome and management of persistent low-level viraemia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. *Antivir Ther*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24964403>.
7. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. 2013;57(10):1489-1496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23946221>.

8. Vandenhende MA, Perrier A, Bonnet F, et al. Risk of virological failure in HIV-1-infected patients experiencing low-level viraemia under active antiretroviral therapy (ANRS C03 cohort study). *Antivir Ther*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25735799>.
9. Pernas B, Grandal M, Pertega S, et al. Any impact of blips and low-level viraemia episodes among HIV-infected patients with sustained virological suppression on ART? *J Antimicrob Chemother*. 2016;71(4):1051-1055. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26702924>.
10. Fleming J, Mathews WC, Rutstein RM, et al. Low-level viremia and virologic failure in persons with HIV infection treated with antiretroviral therapy. *AIDS*. 2019;33(13):2005-2012. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31306175>.
11. Lee KJ, Shingadia D, Pillay D, et al. Transient viral load increases in HIV-infected children in the U.K. and Ireland: what do they mean? *Antivir Ther*. 2007;12(6):949-956. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17926649>.
12. Coovadia A, Abrams EJ, Stehla R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA*. 2010;304(10):1082-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823434>.
13. Grennan JT, Loutfy MR, Su D, et al. Magnitude of virologic blips is associated with a higher risk for virologic rebound in HIV-infected individuals: a recurrent events analysis. *J Infect Dis*. 2012;205(8):1230-1238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22438396>.
14. Karlsson AC, Younger SR, Martin JN, et al. Immunologic and virologic evolution during periods of intermittent and persistent low-level viremia. *AIDS*. 2004;18(7):981-989. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15096800>.
15. Aleman S, Soderbarg K, Visco-Comandini U, Sitbon G, Sonnerborg A. Drug resistance at low viraemia in HIV-1-infected patients with antiretroviral combination therapy. *AIDS*. 2002;16(7):1039-1044. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11953470>.
16. Krogstad P, Patel K, Karalius B, et al. Incomplete immune reconstitution despite virologic suppression in HIV-1 infected children and adolescents. *AIDS*. 2015;29(6):683-693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25849832>.
17. Resino S, Alvaro-Meca A, de Jose MI, et al. Low immunologic response to highly active antiretroviral therapy in naive vertically human immunodeficiency virus type 1-infected children with severe immunodeficiency. *Pediatr Infect Dis J*. 2006;25(4):365-368. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16567992>.
18. Lewis J, Walker AS, Castro H, et al. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: effects on long-term T-cell reconstitution. *J Infect Dis*. 2012;205(4):548-556. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22205102>.
19. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. 2012;26(4):465-474. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22112603>.
20. Claassen CW, Diener-West M, Mehta SH, Thomas DL, Kirk GD. Discordance between CD4+ T-lymphocyte counts and percentages in HIV-infected persons with liver fibrosis. *Clin Infect Dis*. 2012;54(12):1806-1813. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22460963>.
21. Smith K, Kuhn L, Coovadia A, et al. Immune reconstitution inflammatory syndrome among HIV-infected South African infants initiating antiretroviral therapy. *AIDS*. 2009;23(9):1097-1107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19417581>.
22. Meintjes G, Lynen L. Prevention and treatment of the immune reconstitution inflammatory syndrome. *Curr Opin HIV AIDS*. 2008;3(4):468-476. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19373007>.
23. Graham SM. Non-tuberculosis opportunistic infections and other lung diseases in HIV-infected infants and children. *Int J Tuberc Lung Dis*. 2005;9(6):592-602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15971385>.
24. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65(1):65-70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18195140>.
25. Patel K, Ming X, Williams PL, et al. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. *AIDS*. 2009;23(14):1893-1901. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19644348>.

26. van Zyl GU, van der Merwe L, Claassen M, et al. Protease inhibitor resistance in South African children with virologic failure. *Pediatr Infect Dis J*. 2009;28(12):1125-1127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19779394>.
27. Zheng Y, Hughes MD, Lockman S, et al. Antiretroviral therapy and efficacy after virologic failure on first-line boosted protease inhibitor regimens. *Clin Infect Dis*. 2014;59(6):888-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24842909>.
28. Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS*. 2009;23(17):2289-2300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19710593>.
29. Steigbigel RT, Cooper DA, Teppler H, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin Infect Dis*. 2010;50(4):605-612. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20085491>.
30. De Luca A, Di Giambenedetto S, Cingolani A, Bacarelli A, Ammassari A, Cauda R. Three-year clinical outcomes of resistance genotyping and expert advice: extended follow-up of the Argenta trial. *Antivir Ther*. 2006;11(3):321-327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16759048>.
31. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Bein Community Programs for Clinical Research on AIDS. *AIDS*. 2000;14(9):F83-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10894268>.
32. Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS*. 2002;16(2):209-218. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11807305>.
33. Lin D, Seabrook JA, Matsui DM, King SM, Rieder MJ, Finkelstein Y. Palatability, adherence and prescribing patterns of antiretroviral drugs for children with human immunodeficiency virus infection in Canada. *Pharmacoepidemiol Drug Saf*. 2011;20(12):1246-1252. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21936016>.
34. Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med*. 2014;371(3):234-247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25014688>.
35. Kanters S, Socias ME, Paton NI, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. *Lancet HIV*. 2017;4(10):e433-e441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28784426>.
36. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, Phase 3b trial. *Lancet Infect Dis*. 2019;19(3):253-264. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30732940>.
37. Briand C, Dollfus C, Faye A, et al. Efficacy and tolerance of dolutegravir-based combined ART in perinatally HIV-1-infected adolescents: a French multicentre retrospective study. *J Antimicrob Chemother*. 2017;72(3):837-843. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27999017>.
38. Nachman S, Alvero C, Teppler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a Phase 1/2 open label, non-randomised, multicentre trial. *Lancet HIV*. 2018;5(12):e715-e722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30527329>.
39. Harrison L, Melvin A, Fiscus S, et al. HIV-1 drug resistance and second-line treatment in children randomized to switch at low versus higher RNA thresholds. *J Acquir Immune Defic Syndr*. 2015;70(1):42-53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26322666>.
40. MacBrayne CE, Rutstein R, Yogev R, et al. Etravirine pharmacokinetics in treatment-experienced children ages 1- <6 years. Abstract 465. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/etravirine-pharmacokinetics-treatment-experienced-children-ages-1-6>.
41. Meyers T, Sawry S, Wong JY, et al. Virologic failure among children taking lopinavir/ritonavir-containing first-line antiretroviral therapy in South Africa. *Pediatr Infect Dis J*. 2015;34(2):175-179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25741970>.
42. Galan I, Jimenez JL, Gonzalez-Rivera M, et al. Virological phenotype switches under salvage therapy with lopinavir-

- ritonavir in heavily pretreated HIV-1 vertically infected children. *AIDS*. 2004;18(2):247-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15075542>.
43. Ramos JT, De Jose MI, Duenas J, et al. Safety and antiviral response at 12 months of lopinavir/ritonavir therapy in human immunodeficiency virus-1-infected children experienced with three classes of antiretrovirals. *Pediatr Infect Dis J*. 2005;24(10):867-873. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16220083>.
  44. Resino S, Bellon JM, Munoz-Fernandez MA, Spanish Group of HIV Infection. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother*. 2006;57(3):579-582. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16446377>.
  45. Violari A, Bologna R, Kumarasamy N, et al. Safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients: week 48 results of the ARIEL trial. *Pediatr Infect Dis J*. 2015;34(5):e132-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25719453>.
  46. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS*. 2009;23(15):2005-2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19724191>.
  47. Viani RM, Alvero C, Fenton T, et al. Safety, Pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-week results from IMPAACT P1093. *Pediatr Infect Dis J*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26244832>.
  48. Tsiang M, Jones GS, Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent HIV-1 integrase strand transfer inhibitor with an improved resistance profile. *Antimicrob Agents Chemother*. 2016;60(12):7086-7097. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27645238>.
  49. Viani RM, Ruel T, Alvero C, et al. Long-Term Safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: results of the IMPAACT P1093 Study. *J Pediatric Infect Dis Soc*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30951600>.
  50. Agwu AL, Yao TJ, Eshleman SH, et al. Phenotypic co-receptor tropism in perinatally HIV-infected youth failing antiretroviral therapy. *Pediatr Infect Dis J*. 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27078121>.
  51. Huerta-Garcia G, Vazquez-Rosales JG, Mata-Marin JA, Peregrino-Bejarano L, Flores-Ruiz E, Solorzano-Santos F. Genotype-guided antiretroviral regimens in children with multidrug-resistant HIV-1 infection. *Pediatr Res*. 2016;80(1):54-59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26999770>.
  52. Kirk BL, Gomila A, Matshaba M, et al. Early Outcomes of darunavir- and/or raltegravir-based antiretroviral therapy in children with multidrug-resistant HIV at a pediatric center in Botswana. *J Int Assoc Provid AIDS Care*. 2013;12(2):90-94. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23315674>.
  53. Thuret I, Chaix ML, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS*. 2009;23(17):2364-2366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19823069>.
  54. Capetti AF, Sterrantino G, Cossu MV, et al. Salvage therapy or simplification of salvage regimens with dolutegravir plus ritonavir-boosted darunavir dual therapy in highly cART-experienced subjects: an Italian cohort. *Antivir Ther*. 2016. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27661787>.
  55. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis*. 2005;41(2):236-242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15983922>.
  56. Nijhuis M, Schuurman R, de Jong D, et al. Lamivudine-resistant human immunodeficiency virus type 1 variants (184V) require multiple amino acid changes to become co-resistant to zidovudine in vivo. *J Infect Dis*. 1997;176(2):398-405. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9237704>.
  57. Ross L, Parkin N, Chappey C, et al. Phenotypic impact of HIV reverse transcriptase M184I/V mutations in combination with single thymidine analog mutations on nucleoside reverse transcriptase inhibitor resistance. *AIDS*. 2004;18(12):1691-1696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15280780>.
  58. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J*. 2007;26(9):799-805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17721374>.
  59. Zhang X, Lin T, Bertasso A, et al. Population pharmacokinetics of enfuvirtide in HIV-1-infected pediatric patients over 48 weeks of treatment. *J Clin Pharmacol*. 2007;47(4):510-517. Available at: <http://www.ncbi.nlm.nih.gov/>

[pubmed/17389560](https://pubmed/17389560).

60. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J*. 2005;24(10):874-879. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16220084>.
61. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J*. 2008;27(7):623-628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18520443>.
62. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother*. 2008;52(9):3276-3283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18625762>.
63. King JR, Acosta EP, Chadwick E, et al. Evaluation of multiple drug therapy in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J*. 2003;22(3):239-244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12634585>.
64. Emu B, Fessel J, Schrader S, et al. Phase 3 Study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med*. 2018;379(7):645-654. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30110589>.
65. Imaz A, Llibre JM, Mora M, et al. Efficacy and safety of nucleoside reverse transcriptase inhibitor-sparing salvage therapy for multidrug-resistant HIV-1 infection based on new-class and new-generation antiretrovirals. *J Antimicrob Chemother*. 2011;66(2):358-362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21172789>.
66. Tashima KT, Smeaton LM, Fichtenbaum CJ, et al. HIV salvage therapy does not require nucleoside reverse transcriptase inhibitors: a randomized, controlled trial. *Ann Intern Med*. 2015;163(12):908-917. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26595748>.
67. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/13679531>.
68. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther*. 2008;83(2):300-306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17609682>.
69. Wong FL, Hsu AJ, Pham PA, Siberry GK, Hutton N, Agwu AL. Antiretroviral treatment strategies in highly treatment experienced perinatally HIV-infected youth. *Pediatr Infect Dis J*. 2012;31(12):1279-1283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22926213>.
70. Agwu AL, Warshaw MG, McFarland EJ, et al. Decline in CD4 T lymphocytes with monotherapy bridging strategy for non-adherent adolescents living with HIV infection: Results of the IMPAACT P1094 randomized trial. *PLoS One*. 2017;12(6):e0178075. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28604824>.
71. Saitoh A, Foca M, Viani RM, et al. Clinical outcomes after an unstructured treatment interruption in children and adolescents with perinatally acquired HIV infection. *Pediatrics*. 2008;121(3):e513-521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18310171>.
72. Fairlie L, Karalius B, Patel K, et al. CD4+ and viral load outcomes of antiretroviral therapy switch strategies after virologic failure of combination antiretroviral therapy in perinatally HIV-infected youth in the United States. *AIDS*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26182197>.

## Antiretroviral Treatment Interruption in Children with HIV (Last updated April 14, 2020, last reviewed April 14, 2020)

### Panel's Recommendations

- Outside the context of clinical trials, structured interruptions of antiretroviral therapy **are not recommended** for children (**All**).

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

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

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

### Unplanned Treatment Interruptions

Temporary discontinuation of antiretroviral therapy (ART) may be unavoidable in some situations, such as in cases of serious treatment-related toxicity, acute illnesses, or planned surgeries that preclude oral intake. Lack of available medication 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.<sup>1-3</sup> In a retrospective study of 483 children in the ANRS French national pediatric cohort, 42% of participants had treatment interruptions of  $\geq 3$  months (with a median of 12.1 months). Interruption was associated with lower CD4 T lymphocyte (CD4) cell percentages after 4 years, even in those who restarted therapy.<sup>4</sup> 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.<sup>5</sup>

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 duration, 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

Structured treatment interruptions are scheduled periods of time during which ART is not prescribed or administered. This strategy was once considered a method for providing patients with time off ART in order to reduce the risk of toxicity and costs. Randomized clinical trials of adults with HIV have demonstrated that structured treatment interruptions are associated with significantly higher morbidity and mortality compared to continuous ART.<sup>6</sup> 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 children (34%) in the structured treatment interruption arm met CD4 criteria to restart therapy between 6 and 42 weeks after interruption, suggesting that the time off ART provided by this strategy was ultimately limited.<sup>7,8</sup> 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 decline. The median time to the start of continuous ART after interruption was 33 weeks (interquartile range [IQR] 26–45 weeks) among the infants who discontinued ART after 40 weeks, and 70 weeks (IQR 35–109 weeks) among the infants who discontinued ART after 96 weeks.<sup>9,10</sup> A secondary analysis of neurodevelopmental outcomes at age 5 years did not show any significant differences among the children in the different study arms.<sup>11</sup> 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 ART without interruption.<sup>12</sup> In another randomized trial, 12 of 21 infants in the treatment interruption arm met ART restart criteria within 3 months.<sup>13</sup> 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 HIV Infection](#)).<sup>14,15</sup> However, the “Mississippi infant” had documented viral rebound after 28 months off ART,<sup>16</sup> 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.<sup>17,18</sup> **A South African child aged 9.5 years was reported to have low levels of virus that was not replication competent after receiving ART from around 2 to 24 months of age; the factors that lead to this outcome remain unknown.**<sup>19</sup>

Future research might identify treatment strategies and diagnostic tests that enable ART to be safely interrupted in some children. **“Analytical” treatment interruptions are currently being incorporated into studies of remission in adults and children, but the potential risks and benefits of strategies need to be critically evaluated.**<sup>20,21</sup> 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 **in clinical settings** to confirm diagnosis or to assess remission or cure in infants who reverted to negative serology, tested negative for HIV DNA, or received an initial diagnosis that was based on a single positive nucleic acid test. The Panel encourages providers to consult an expert on pediatric HIV when they are concerned about the validity of the test results that led to treatment initiation in children with HIV.

### ***Short-Cycle Therapy Strategies***

One approach, called short-cycle therapy (SCT), schedules 4-day treatment interruptions, rather than waiting to restart ART after CD4 count declines or other AEs occur. In one proof-of-concept study (ATN015), 32 participants (aged 12–24 years) underwent short cycles of 4 days on and 3 days off ART.<sup>22</sup> Participants had at least 6 months of documented viral suppression (defined as a viral load <400 copies/mL), CD4 counts above 350 cells/mm<sup>3</sup>, 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 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 8–24 years) to receive SCT (5 days on and 2 days off ART) or CT.<sup>23,24</sup> To enroll, participants had to be receiving efavirenz (EFV) plus two nucleoside reverse transcriptase inhibitors, and they had to have been virologically suppressed (defined as a viral load <50 copies/mL) for >12 months. By 48 weeks, six participants (6%) in the SCT arm and seven participants (7%) in the CT arm experienced confirmed virologic failure, which was defined as a viral load >50 copies/mL (difference -1.2%; 90% confidence interval, -7.3% to 4.9%). Of the six participants in the SCT arm who experienced virologic failure, five were able to regain virologic suppression. Two participants in the SCT arm and five participants in the CT arm had major mutations related to resistance to non-nucleoside reverse

transcriptase inhibitors at the time of virologic failure. At 48 weeks, the SCT arm had higher d-dimer levels but no other evidence of increased inflammation across a number of other biomarkers. Participants generally reported appreciating the option of SCT.<sup>25</sup>

A long-term follow-up study of children from the BREATHER study (which included 194 of the original 199 children) suggests comparable virologic failure rates between the SCT and CT arms after a median of 3.6 years; both arms had a failure rate of approximately 16%.<sup>26</sup> 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 the primary difference being rate by of 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 EFV-based ART may be safe in some adolescents and may yield increased patient satisfaction that could lead to better long-term adherence. However, the Panel believes that additional data are needed to decide whether this strategy would be safe in different patient populations, with different antiretroviral (ARV) regimens, outside of the context of a trial, and over longer periods 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. One of the benefits of treatment interruptions was the potential reduction of toxicity; however, current ARV agents have lower toxicity than older ARV drugs. It is possible that SCT strategies may be safe for some patients, but additional data are needed to support the use of these strategies. 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.

## References

1. Gibb DM, Duong T, Leclezio VA, et al. Immunologic changes during unplanned treatment interruptions of highly active antiretroviral therapy in children with human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J*. 2004;23(5):446-450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15131469>.
2. Saitoh A, Foca M, Viani RM, et al. Clinical outcomes after an unstructured treatment interruption in children and adolescents with perinatally acquired HIV infection. *Pediatrics*. 2008;121(3):e513-521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18310171>.
3. Siberry GK, Patel K, Van Dyke RB, et al. CD4+ lymphocyte-based immunologic outcomes of perinatally HIV-infected children during antiretroviral therapy interruption. *J Acquir Immune Defic Syndr*. 2011;57(3):223-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21423022>.
4. Aupiais C, Faye A, Le Chenadec J, et al. Interruption of cART in clinical practice is associated with an increase in the long-term risk of subsequent immunosuppression in HIV-1-infected children. *Pediatr Infect Dis J*. 2014;33(12):1237-1245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24945880>.
5. Rakhmanina N, Lam KS, Hern J, Young HA, Walters A, Castel AD. Interruptions of antiretroviral therapy in children and adolescents with HIV infection in clinical practice: a retrospective cohort study in the USA. *J Int AIDS Soc*. 2016;19(1):20936. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27797320>.
6. Strategies for Management of Antiretroviral Therapy Study G, El-Sadr WM, Lundgren JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17135583>.
7. Paediatric European Network for Treatment of AIDS. Response to planned treatment interruptions in HIV infection varies across childhood. *AIDS*. 2010;24(2):231-241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20010073>.
8. Bunupuradah T, Duong T, Compagnucci A, et al. Outcomes after reinitiating antiretroviral therapy in children randomized to planned treatment interruptions. *AIDS*. 2013;27(4):579-589. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23135172>.

9. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233-2244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19020325>.
10. Cotton MF, Violari A, Otwombe K, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. *Lancet*. 2013;382(9904):1555-1563. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24209829>.
11. Laughton B, Cornell M, Kidd M, et al. Five year neurodevelopment outcomes of perinatally HIV-infected children on early limited or deferred continuous antiretroviral therapy. *J Int AIDS Soc*. 2018;21(5):e25106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29722482>.
12. Nwosu E, Holmes M, Cotton M, et al. Antiretroviral therapy (ART) interruption is associated with reduced cortical structures at age 5 years compared to uninterrupted. International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_11.htm](http://www.natap.org/2018/IAC/IAC_11.htm).
13. Wamalwa D, Benki-Nugent S, Langat A, et al. Treatment interruption after 2-year antiretroviral treatment initiated during acute/early HIV in infancy. *AIDS*. 2016;30(15):2303-2313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27177316>.
14. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013;369(19):1828-1835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24152233>.
15. Persaud D, Luzuriaga K. Absence of HIV-1 after treatment cessation in an infant. *N Engl J Med*. 2014;370(7):678. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24521123>.
16. Luzuriaga K, Gay H, Ziemniak C, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. *N Engl J Med*. 2015;372(8):786-788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25693029>.
17. Mekonen T, Mulang R, Nghimbwasha H, et al. Structured antiretroviral treatment interruptions in vertically HIV-1 infected children with complete pro-viral DNA PCR reversions in Namibia, following durable viral suppression, led to rapid rebound viremias and significant immunologic destruction. Presented at: International AIDS Conference. 2016. Durban, South Africa.
18. Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. *Pediatr Infect Dis J*. 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25251719>.
19. Violari A, Cotton MF, Kuhn L, et al. A child with perinatal HIV infection and long-term sustained virological control following antiretroviral treatment cessation. *Nat Commun*. 2019;10(1):412. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30679439>.
20. National Institute of Allergy and Infectious Diseases. Very early intensive treatment of HIV-infected infants to achieve HIV remission. 2019. Available at: <https://clinicaltrials.gov/ct2/show/NCT02140255>.
21. Julg B, Dee L, Ananworanich J, et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting. *Lancet HIV*. 2019;6(4):e259-e268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30885693>.
22. Rudy BJ, Slesman J, Kapogiannis B, et al. Short-cycle therapy in adolescents after continuous therapy with established viral suppression: the impact on viral load suppression. *AIDS Res Hum Retroviruses*. 2009;25(6):555-561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19534628>.
23. Butler K, Inshaw J, Ford D, et al. BREATHER (PENTA 16) short-cycle therapy (SCT) (5 days on/2 days off) in young people with chronic human immunodeficiency virus infection: an open, randomised, parallel-group Phase II/III trial. *Health Technol Assess*. 2016;20(49):1-108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27377073>.
24. Group BT. Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents, and young adults (BREATHER): a randomised, open-label, non-inferiority, phase 2/3 trial. *Lancet HIV*. 2016;3(9):e421-e430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27562743>.
25. Bernays S, Papparini S, Seeley J, Namukwaya Kihika S, Gibb D, Rhodes T. Qualitative study of the BREATHER trial (short cycle antiretroviral therapy): is it acceptable to young people living with HIV? *BMJ Open*. 2017;7(2):e012934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28213595>.
26. Turkova A, Moore CL, Butler K, et al. Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents and young adults (BREATHER): Extended follow-up results of a randomised, open-label, non-inferiority trial. *PLoS One*. 2018;13(4):e0196239. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29684092>.

## **Appendix A: Pediatric Antiretroviral Drug Information**

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### **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 14, 2020; last reviewed April 14, 2020)

### Formulations

**Pediatric Oral Solution:** 20 mg/mL

**Tablet:** 300 mg (scored)

#### Generic Formulations:

- 300 mg tablet
- 20 mg/mL pediatric oral solution

#### Fixed-Dose Combination Tablets:

- [Epzicom and generic] Abacavir 600 mg/lamivudine 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Neonate and Infant Dose:

- Abacavir (ABC) is not approved for use in infants aged <3 months

#### Infant and Child (Aged ≥3 Months) Dose

##### Oral Solution:

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

### 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 ABC. Patients with no prior HLA-B\*5701 testing who are tolerating ABC do not need to be tested.
- Warn patients and caregivers about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of ABC. Do not rechallenge.**
- ABC can be given without regard to food. The oral solution does not require refrigeration.
- Screen patients for hepatitis B virus (HBV) infection before using Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets). These FDC tablets contain lamivudine (3TC), and severe acute

### Weight-Band Dosing for Children and Adolescents Weighing $\geq 14$ kg

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

#### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose:

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

#### [Epzicom] Abacavir/Lamivudine

Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:

- One tablet once daily

#### [Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:

- One tablet once daily
- This FDC tablet can be used in patients who are antiretroviral (ARV)-naive or ARV-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The Food and Drug Administration-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg (see the [Dolutegravir](#) section for more information).

#### [Trizivir] Abacavir/Lamivudine/Zidovudine

Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:

- One tablet twice daily

exacerbation of HBV infection can occur when 3TC is discontinued. Therefore, hepatic function and hepatitis B viral load should be monitored for several months after therapy with 3TC is stopped in patients with HBV.

### Metabolism/Elimination

- ABC is systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.
- The majority of ABC is excreted as metabolites in urine.
- ABC requires a dose adjustment in patients with hepatic insufficiency.
- **Do not use** FDC tablets such as Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets) in patients with impaired hepatic function, because the dose of ABC cannot be adjusted.
- **Do not use** Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets) in patients with creatinine clearance  $< 50$  mL/min and patients on dialysis, because the dose of 3TC cannot be adjusted.

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

- Abacavir (ABC) 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.
- ABC plasma concentrations can decrease when ABC is used concurrently with the boosted PIs atazanavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir.<sup>1-3</sup> 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 ABC 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 ABC metabolism by affecting the activity of alcohol dehydrogenase and glucuronyl transferase. This interference led to a 41% increase in ABC area under the curve plasma exposure in adult men with HIV who received ABC 600 mg daily.<sup>4</sup>
- ABC oral solution contains sorbitol, which decreased the exposure of lamivudine (3TC) oral solution in adults when the drugs were administered concurrently.<sup>5</sup>

### **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) who were receiving ABC. The HSR to ABC 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 ABC. If an HSR is suspected, ABC **should be stopped immediately and not restarted—hypotension and death may occur upon rechallenge.** The risk of an ABC HSR is associated with the presence of the HLA-B\*5701 allele; the risk is greatly reduced by not using ABC in those who test positive for the HLA-B\*5701 allele.
- *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 that there is an increased risk of myocardial infarction in adults who are currently using ABC or who have recently used ABC; however, other studies have not substantiated this finding, and there are no **prospective** data on the cardiovascular risks that are associated with ABC use in children. One cohort study of South African adolescents (in which 385 participants had HIV and 63 participants were HIV-negative controls) with a median age of 12 years reported an association between ABC exposure and insulin resistance, which was evaluated using homeostatic model assessment. These findings suggest that the use of ABC may be a cardiovascular risk factor for young people with perinatally acquired HIV.<sup>6</sup>

### **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*

ABC is approved by the Food and Drug Administration (FDA) for use in children with HIV aged  $\geq 3$  months

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as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The World Health Organization (WHO), however, recommends using ABC as a component of the NRTI backbone for children weighing  $\geq 3$  kg, starting at 4 weeks of age (see [Dosages of Antiretroviral Drugs from WHO](#)). 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 ABC formulations, including coformulations that include 3TC, and the cost of antiretroviral (ARV) drugs in resource-limited settings. No systematic safety assessment has been conducted for using ABC in children weighing  $< 14$  kg.

### *Efficacy*

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

### **Pharmacokinetics**

#### *Pharmacokinetics in Children*

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

The PKs of ABC administered once daily in children with HIV aged 3 months through 12 years were evaluated in three crossover, open-label PK trials of twice-daily versus once-daily dosing of ABC and 3TC (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).<sup>4,13-16</sup> The data from these three pediatric trials were used to develop a model for ABC PKs; this model predicted that systemic plasma ABC exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged  $\leq 12$  years.<sup>13-17</sup> Both these trials and PK modeling have demonstrated that once-daily dosing with either the tablet or the liquid formulation of ABC produces plasma exposures that are comparable to those seen with a twice-daily dosing schedule that uses the same total daily dose of ABC.<sup>18</sup>

### **Dosing**

#### *Dosing and Formulations*

Initially, the recommended dose for pediatric use was ABC 8 mg/kg twice daily, for a total of 16 mg/kg per day. A 2015 FDA review suggested that a total daily dose of ABC 600 mg could be safely used in a person weighing 25 kg (i.e., ABC 24 mg/kg per day, a 50% increase from the previously recommended dose). The weight-band dosing table recommends total daily doses as high as ABC 21.5 mg/kg per day to ABC 22.5 mg/kg per day when treating patients with the tablet formulation.<sup>4</sup> There is no difference in the ABC plasma  $C_{max}$  and area under the curve for the ABC liquid formulation compared to the tablet formulation.<sup>19</sup> Doses of the liquid ABC formulation are similar to those used for weight-band dosing with tablet formulations and should be considered for use in younger children who are unable to swallow a pill.

In all three ABC dosing pediatric trials described above,<sup>13-16</sup> only children who had low viral loads and who were clinically stable on the twice-daily dose of ABC were eligible to change to once-daily ABC dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical noninferiority of once-daily ABC (n = 336) versus twice-daily ABC (n = 333) in tablet form combined with a once-daily or twice-daily 3TC-based ARV regimen.<sup>9</sup> To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of the ABC liquid formulation. In children who can be treated with pill formulations, initiating therapy with once-daily dosing of ABC at a dose of 16 mg/kg (with a maximum dose of ABC 600 mg) is recommended. However, twice-daily dosing is recommended for infants and young children who initiate therapy with the liquid formulation of ABC. Switching to once-daily dosing with the liquid or pill formulation could be considered in clinically stable children with suppressed viral loads and stable CD4 T lymphocyte cell counts.

## Toxicity

ABC has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,<sup>7,8</sup> and less bone and renal toxicity than tenofovir disoproxil fumarate.<sup>20,21</sup>

## References

1. Waters LJ, Moyle G, Bonora S, et al. Abacavir plasma pharmacokinetics in the absence and presence of atazanavir/ritonavir or lopinavir/ritonavir and vice versa in HIV-infected patients. *Antivir Ther.* 2007;12(5):825-830. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17713166>.
2. Pruvost A, Negredo E, Theodoro F, et al. Pilot pharmacokinetic study of human immunodeficiency virus-infected patients receiving tenofovir disoproxil fumarate (TDF): investigation of systemic and intracellular interactions between TDF and abacavir, lamivudine, or lopinavir-ritonavir. *Antimicrob Agents Chemother.* 2009;53(5):1937-1943. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19273671>.
3. Jackson A, Moyle G, Dickinson L, et al. Pharmacokinetics of abacavir and its anabolite carbovir triphosphate without and with darunavir/ritonavir or raltegravir in HIV-infected subjects. *Antivir Ther.* 2012;17(1):19-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22267465>.
4. Abacavir [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/020977s033s034,020978s036s037lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020977s033s034,020978s036s037lbl.pdf).
5. Adkinson K, McCoig C, Wolstenholme A, et al. Effect of sorbitol on lamivudine pharmacokinetics following administration of EPIVIR® solution in adults. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
6. Frigati LJ, Jao J, Mahtab S, et al. Insulin resistance in South African youth living with perinatally acquired HIV receiving antiretroviral therapy. *AIDS Res Hum Retroviruses.* 2019;35(1):56-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30156434>.
7. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without neftinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002;359(9308):733-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11888583>.
8. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS.* 2007;21(8):947-955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17457088>.
9. Musiime V, Kasirye P, et al. Randomised comparison of once versus twice daily abacavir and lamivudine among 669 HIV-infected children in the ARROW trial. Presented at: Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, Georgia.
10. Adetokunboh OO, Schoonees A, Balogun TA, Wiysonge CS. Efficacy and safety of abacavir-containing combination antiretroviral therapy as first-line treatment of HIV infected children and adolescents: a systematic review and meta-analysis. *BMC Infect Dis.* 2015;15:469. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26502899>.
11. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis.* 2016;16(2):169-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26481928>.
12. Sleasman JW, Robbins BL, Cross SJ, et al. Abacavir pharmacokinetics during chronic therapy in HIV-1-infected adolescents and young adults. *Clin Pharmacol Ther.* 2009;85(4):394-401. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19118380>.
13. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J.* 2006;25(6):533-537. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16732152>.
14. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther.*

2005;10(2):239-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15865218>.

15. Paediatric European Network for Treatment of AIDS. Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-<36 months. *Antivir Ther*. 2010;15(3):297-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20516550>.
16. Musiime V, Kendall L, Bakeera-Kitaka S, et al. Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. *Antivir Ther*. 2010;15(8):1115-1124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21149918>.
17. Zhao W, Piana C, Danhof M, Burger D, Pasqua OD, Jacqz-Aigrain E. Population pharmacokinetics of abacavir in infants, toddlers and children. *Br J Clin Pharmacol*. 2013;75(6):1525-35. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23126277>.
18. Food and Drug Administration. FDA approved revisions to the Epivir (lamivudine) and Ziagen (abacavir sulfate) labels. 2015.
19. Kasirye P, Kendall L, Adkison KK, et al. Pharmacokinetics of antiretroviral drug varies with formulation in the target population of children with HIV-1. *Clin Pharmacol Ther*. 2012;91(2):272-280. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22190066>.
20. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr*. 2010;55(1):49-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20431394>.
21. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS clinical trials group A5224s, a substudy of ACTG A5202. *J Infect Dis*. 2011;203(12):1791-1801. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21606537>.

## Emtricitabine (FTC, Emtriva) (Last updated April 14, 2020; last reviewed April 14, 2020)

### 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 300 mg
- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg
- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Descovy] Emtricitabine 200 mg/tenofovir alafenamide 25 mg
- [Genvoya] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg
- [Truvada] Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Truvada low-strength tablets]
  - Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg
  - Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg
  - Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

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

*Oral Solution:*

- Emtricitabine (FTC) 3 mg/kg once daily

#### Child (Aged ≥3 Months) and Adolescent Dose

*Oral Solution:*

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

*Capsules (For Patients Weighing >33 kg):*

- FTC 200 mg once daily

#### Adult Dose

*Oral Solution for Patients Who Are Unable to Swallow Capsules:*

- FTC 240 mg (24 mL) once daily

### Selected Adverse Events

- Hyperpigmentation/skin discoloration on palms and/or soles

### Special Instructions

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

### Capsules:

- FTC 200 mg once daily

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

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

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

### [Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (TAF)

#### **Child (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. **Studies are currently being conducted to identify the appropriate dose for this age and weight group.**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily **with or without food** 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 mutations associated with resistance to the individual components of Biktarvy.
- See the [Bictegravir](#) section for additional information.

### [Complera] Emtricitabine/Rilpivirine/TDF

*Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily in ART-naive patients who have baseline plasma HIV RNA  $\leq 100,000$  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 treatment failure and no known mutations associated with resistance to the individual components of Complera.
- Administer with a meal of at least 500 calories.

### [Descovy] Emtricitabine/TAF

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

## Metabolism/Elimination

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

### Emtricitabine Dosing in Patients with Renal Impairment:

- Decrease the dose of FTC in patients with impaired renal function. Consult the manufacturer's prescribing information for recommended dose adjustments.
- **Do not use** the FDC tablet Atripla in patients with creatinine clearance (CrCl)  $< 50$  mL/min or in patients who require dialysis.
- **Do not use** the FDC tablets Truvada or Biktarvy in patients with CrCl  $< 30$  mL/min. Do not use Truvada in patients who require dialysis.
- 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.

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  $\geq$ 35 kg:

- One tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

**[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/TAF**

*Child and Adolescent (Weighing  $\geq$ 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 mutations associated with resistance to the individual components of Genvoya.

**[Odefsey] Emtricitabine/Rilpivirine/TAF**

*Child and Adolescent (Aged  $\geq$ 12 Years and Weighing  $\geq$ 35 kg) and Adult Dose:*

- One tablet once daily in ART-naive patients with HIV RNA  $\leq$ 100,000 copies per mL. This dose of Odefsey can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.
- Administer with a meal of at least 500 calories.

**[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF**

*Child and Adolescent (Weighing  $\geq$ 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 the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) for at

least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.

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

Child and Adolescent (**Weighing  $\geq 40$  kg**) and Adult Dose:

- One tablet once daily with food in ART-naive patients or in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months with no known mutations associated with resistance to darunavir or tenofovir.

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

Child, Adolescent, and Adult Dose:

**Truvada Dosing Table**

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

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

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* **Do not use** emtricitabine (FTC) in combination with lamivudine (3TC), because these agents share similar resistance profiles and lack additive benefit. **Do not use FTC** with fixed-dose combination (FDC) medications that contain 3TC or FTC. 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 an FDC tablet.
- *Renal elimination:* FTC may compete with other compounds that undergo renal tubular secretion. Drugs that decrease renal function could decrease clearance of FTC.

**Major Toxicities**

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

**Resistance**

The International Antiviral Society-USA (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***

FTC is approved by the Food and Drug Administration for once-daily administration in children, starting at birth. FTC 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 that assess the efficacy and/or potency of nucleoside/nucleotide analogues have been more concerned with the dynamic components of the regimen, such as tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or abacavir, than the more static components, such as FTC or 3TC. FTC and 3TC have been considered to be interchangeable, but there is a lack of data to support this conclusion. Investigators studying the ATHENA cohort compared the efficacy of TDF plus FTC to TDF plus 3TC when these drugs were administered with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ART-naïve patients.<sup>1</sup> The adjusted hazard ratio for the virologic failure of 3TC-containing regimens compared to FTC-containing regimens within 240 weeks of starting therapy was 1.15 (95% confidence interval, 0.58–2.27). There was no difference between these regimens in time to virologic suppression during the first 48 weeks of therapy or time to virologic failure after attaining suppression. In a Swiss cohort, Yang et al. found a potential difference in efficacy between FTC and 3TC; however, the difference disappeared after adjusting for pill burden.<sup>2</sup> Current evidence suggests that FTC and 3TC have equivalent efficacy and toxicity in ARV-naïve patients.

#### ***Efficacy***

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

#### ***Pharmacokinetics: Liquid Versus Capsule***

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

#### ***Pharmacokinetics in Infants***

A study in South Africa evaluated the PKs of FTC in 20 infants aged <3 months with perinatal HIV exposure. The participants received a dose of FTC 3 mg/kg once daily for two 4-day courses, separated by an interval of ≥2 weeks.<sup>6</sup> FTC exposure (area under the curve [AUC]) in neonates receiving FTC 3 mg/kg once daily

was within the range of exposures seen in pediatric patients aged >3 months who received the recommended dose of FTC 6 mg/kg once daily and adults who received the recommended once-daily dose of FTC 200 mg. Over the first 3 months of life, FTC AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (n = 6) who received a single dose of FTC 3 mg/kg and whose mothers received a single dose of FTC 600 mg during delivery, the FTC AUC exceeded the AUC seen in adults and older children. However, FTC had a half-life of 9.2 hours in these neonates, which is similar to that observed in adults and older children.<sup>7</sup> Extensive safety data are lacking for this age range.

### *Considerations for Use*

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

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

## References

1. Rokx C, Gras L, van de Vijver D, Verbon A, Rijnders B, Athena National Observational Cohort Study. Virological responses to lamivudine or emtricitabine when combined with tenofovir and a protease inhibitor in treatment-naïve HIV-1-infected patients in the Dutch AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. *HIV Med.* 2016; 17(8):571-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26842457>.
2. Yang WL, Kouyos RD, Scherrer AU, et al. Assessing efficacy of different nucleos(t)ide backbones in NNRTI-containing regimens in the Swiss HIV cohort study. *J Antimicrob Chemother.* 2015;70(12):3323-3331. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26362944>.
3. Wang LH, Wiznia AA, Rathore MH, et al. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother.* 2004;48(1):183-191. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14693538>.
4. Saez-Llorens X, Violari A, Ndiweni D, et al. Long-term safety and efficacy results of once-daily emtricitabine-based highly active antiretroviral therapy regimens in human immunodeficiency virus-infected pediatric subjects. *Pediatrics.* 2008;121(4):e827-835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18332076>.
5. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naïve children and adolescents: Pediatric AIDS clinical trials group protocol P1021. *Pediatrics.* 2007;120(2):e416-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17646352>.
6. Blum M, Ndiweni D, Chittick Gea. Steady state pharmacokinetic evaluation of emtricitabine in neonates exposed to HIV *in utero*. Presented at: Conference on Retroviruses and Opportunistic Infections. 2006. Denver, Colorado.
7. Flynn PM, Mirochnick M, Shapiro DE, et al. Pharmacokinetics and safety of single-dose tenofovir disoproxil fumarate and emtricitabine in HIV-1-infected pregnant women and their infants. *Antimicrob Agents Chemother.* 2011;55(12):5914-5922. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21896911>.

## Lamivudine (3TC, Epivir) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

#### Pediatric Oral Solution:

- [Epivir] 10 mg/mL
- [Epivir HBV]<sup>a</sup> 5 mg/mL

#### Tablets:

- [Epivir] 150 mg (scored) and 300 mg
- [Epivir HBV]<sup>a</sup> 100 mg

#### Generic Formulations:

- 100 mg, 150 mg, and 300 mg tablets
- Fixed-dose combination (FDC) tablet containing lamivudine 150 mg/zidovudine 300 mg

#### Fixed-Dose Combination Tablets:

- [Cimduo] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg
- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Epzicom] Abacavir 600 mg/lamivudine 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Temixys] Lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using FDC tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and [Table 12](#) for information about using lamivudine (3TC) for the prevention of perinatal HIV transmission.

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

##### Oral Solution:

- 3TC 2 mg/kg twice daily

##### Infant and Child Dose:

- Once-daily dosing of the 3TC oral solution **is not recommended** when initiating 3TC oral solution in infants and young children. Patients can be transitioned to once-daily treatment with the oral solution when they

### Selected Adverse Events

- Severe exacerbation of hepatitis can occur in patients with hepatitis B virus (HBV)/HIV coinfection who discontinue 3TC.

### Special Instructions

- 3TC can be given without regard to food.
- Store 3TC oral solution at room temperature.
- Screen patients for HBV infection before using 3TC or FDC tablets that contain 3TC. **Hepatic function and hepatitis B viral load should be monitored for several months after patients with HBV infection stop taking 3TC. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection.**

have been stable on twice-daily treatment for 36 weeks and are aged  $\geq 3$  years. Please see the note below and refer to the text for more detail.

*Aged  $\geq 4$  Weeks to  $< 3$  Months:*

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

*Aged  $\geq 3$  Months to  $< 3$  Years:*

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

*Aged  $\geq 3$  Years:*

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

**Weight-Band Dosing for the 10 mg/mL Lamivudine Oral Solution in Children Weighing  $\geq 3$  kg**

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM
3 kg to 5.9 kg	3 ml	3 ml
6 kg to 9.9 kg	4 ml	4 ml
10 kg to 13.9 kg	6 ml	6 ml

*Weighing  $\geq 14$  kg and Able to Swallow Tablets:*

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

**Weight-Band Dosing for the Scored, 150-mg Lamivudine Tablet in Children Weighing  $\geq 14$  kg**

Weight	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to $< 20$ kg	$\frac{1}{2}$ tablet (75 mg)	$\frac{1}{2}$ tablet (75 mg)	1 tablet (150 mg)
$\geq 20$ kg to $< 25$ kg	$\frac{1}{2}$ tablet (75 mg)	1 tablet (150 mg)	$1\frac{1}{2}$ tablets (225 mg)
$\geq 25$ kg	1 tablet (150 mg)	1 tablet (150 mg)	2 tablets (300 mg)

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports switching from twice-daily dosing to once-daily dosing of 3TC (using the oral solution or tablets) in children aged  $\geq 3$  years who have been clinically stable for 36 weeks

**Metabolism/Elimination**

- Dose adjustment is required for patients with renal insufficiency.
- FDC tablets should not be used in patients who are on dialysis, patients who have creatinine clearance  $< 50$  mL/min, or patients who have impaired hepatic function.

with undetectable viral loads and stable CD4 T lymphocyte counts. Clinicians should choose a once-daily regimen using the once-daily dose of 3TC indicated above (approximately 3TC 10 mg/kg, with a maximum of 3TC 300 mg once daily).

**Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:**

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

**[Cimduo] Lamivudine/Tenofovir Disoproxil Fumarate (TDF)**

*Child and Adolescent (Weighing  $>35$  kg) and Adult Dose:*

- One tablet once daily

**[Combivir and Generic] Lamivudine/Zidovudine**

*Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:*

- One tablet twice daily

**[Delstrigo] Doravirine/Lamivudine/TDF**

*Adult Dose:*

- One tablet once daily
- The use of Delstrigo has not been studied in children or adolescents (see the [Doravirine](#) section for more information).

**[Dovato] Dolutegravir/Lamivudine**

*Adult Dose:*

- One tablet once daily with or without food as a complete antiretroviral (ARV) regimen in antiretroviral therapy (ART)-naive adults with no known mutations associated with resistance to the individual components of Dovato.
- Dovato is not approved by the Food and Drug Administration (FDA) or recommended by the Panel for use in children or adolescents **as a complete ARV regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug.**

**[Epzicom] Abacavir/Lamivudine**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily

**[Symfi] Efavirenz 600 mg/Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet once daily on an empty stomach

### **[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily on an empty stomach
- Symfi Lo has not been studied in children (sexual maturity ratings [SMRs] 1–3), and major interindividual variability in efavirenz (EFV) plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400 mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh  $\geq 40$  kg. The use of therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh  $\geq 40$  kg. See the [Efavirenz](#) section for more information.

### **[Temixys] Lamivudine/TDF**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily

### **[Triumeq] Abacavir/Dolutegravir/Lamivudine**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily
- This FDC tablet can be used in patients who are ART-naive or ART-experienced (but integrase strand transfer inhibitor-naive) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The FDA-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg (see the [Dolutegravir](#) section for more information).

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

*Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:*

- One tablet twice daily

<sup>a</sup> Eпивir HBV oral solution and tablets contain a lower amount of 3TC than Eпивir oral solution and tablets. The amount of 3TC in the Eпивir HBV solution and tablet was based on dosing for treatment of HBV infection in people without HIV coinfection. Patients with HIV who are taking Eпивir HBV as part of their ARV regimen should receive the appropriate amount of oral solution or the appropriate number of tablets to achieve the higher doses of 3TC that are used to treat HIV.

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

- Drugs that decrease renal function could decrease clearance of lamivudine (3TC).

- **Do not use** 3TC in combination with emtricitabine (FTC), because these drugs have similar resistance profiles and using them together offers no additional benefit.<sup>1</sup> **Do not use** 3TC with fixed-dose combination (FDC) medications that contain 3TC or FTC. Please see [Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets](#) and refer to other sections of the [Drug Appendix](#) for drug interaction information about each individual component of FDC tablets.

### **Major Toxicities**

- *More common:* Headache, nausea.
- *Less common (more severe):* Peripheral neuropathy, lipodystrophy/lipoatrophy.
- *Rare:* Increased levels of liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

### **Resistance**

The International Antiviral Society-USA (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*

3TC is approved by the Food and Drug Administration (FDA) for the treatment of children aged  $\geq 3$  months.

#### *Considerations for Use*

The efficacy and toxicity of 3TC are equivalent to the efficacy and toxicity of FTC. The oral formulation of FTC has an advantage over the liquid formulation of 3TC, since it can be given once daily at antiretroviral (ARV) initiation while the liquid formulation of 3TC needs to be given twice daily at ARV initiation. When pill formulations of 3TC or FTC are used, they can be administered once daily.

#### *Comparative Clinical Trials*

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

#### *Efficacy*

3TC has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data have demonstrated the safety of 3TC and have shown that this drug is associated with clinical improvement and virologic response. It is commonly used in children with HIV as a component of a dual-NRTI backbone.<sup>4-12</sup> In one study that evaluated the efficacy of NRTI background components, the combination of 3TC plus ABC was superior to zidovudine (ZDV) plus 3TC or ZDV plus ABC in achieving long-term virologic efficacy.<sup>13</sup>

### *Pharmacokinetics in Infants*

Because of its safety profile and availability in a liquid formulation, 3TC has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.<sup>9</sup> A population pharmacokinetic (PK) analysis of infants who received 3TC affirms that adjusting the dose from 3TC 2 mg/kg to 3TC 4 mg/kg every 12 hours at age 4 weeks provides optimal 3TC exposure for infants with normal maturation of renal function.<sup>14</sup> For infants, the World Health Organization weight-band dosing (which is up to five times higher than the FDA-approved dose) results in greater plasma concentrations than the 3TC 2 mg/kg dose.<sup>15</sup> In HPTN 040, 3TC was administered with nelfinavir and 6 weeks of ZDV according to a weight-band dosing scheme to prevent perinatal transmission during the first 2 weeks of life. For 2 weeks, all infants weighing >2,000 g received 3TC 6 mg twice daily, and infants weighing ≤2,000 g received 3TC 4 mg twice daily. These doses resulted in 3TC exposure that was similar to the exposure seen in infants who received the standard twice-daily dosing schedule of 3TC 2 mg/kg per dose for neonates.<sup>16</sup>

### *Pharmacokinetics of Liquid versus Tablet Preparations*

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

### *Dosing Considerations—Once-Daily versus Twice-Daily Administration*

The standard adult dose for 3TC is 300 mg once daily, but there is a lack of data on once-daily administration of 3TC in children. Population PK data indicate that once-daily dosing of 3TC 8 mg/kg leads to area under the curve (AUC<sub>0-24h</sub>) values that are similar to those seen in patients taking 3TC 4 mg/kg twice daily, but C<sub>min</sub> values are significantly lower and C<sub>max</sub> values are significantly higher in children aged 1 to 18 years.<sup>19</sup> Intensive PKs of once-daily versus twice-daily dosing of 3TC were evaluated in children with HIV aged 2 to 13 years in the PENTA 13 trial<sup>4</sup> and in children aged 3 to 36 months in the PENTA 15 trial.<sup>20</sup> Both the PENTA 13 and PENTA 15 trials used a crossover design with doses of 3TC 8 mg/kg once daily or 3TC 4 mg/kg twice daily. AUC<sub>0-24</sub> and clearance values were similar between these two dosing schedules, and most children maintained an undetectable HIV RNA value after the switch. An ARROW trial PK study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily 3TC also showed equivalent AUC<sub>0-24h</sub> and good clinical outcomes (defined by a low disease stage and a high CD4 T lymphocyte [CD4] cell count) after switching to once-daily 3TC. Median follow-up time during this study was 1.15 years.<sup>21</sup> The larger ARROW trial was a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of 3TC in >600 pediatric patients who had initiated therapy with twice-daily 3TC and who had been receiving therapy for ≥36 weeks. Median follow-up time during the study was 114 weeks.

Rates of plasma HIV RNA suppression and adverse event profiles for once-daily 3TC were similar to (and statistically noninferior to) those of twice-daily 3TC.<sup>22</sup>

All four of the studies discussed above enrolled patients who had a low plasma HIV RNA or who were clinically stable on twice-daily 3TC before switching to once-daily dosing. Therefore, the Panel supports switching from twice-daily to once-daily dosing of 3TC in children aged  $\geq 3$  years who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 count. Clinicians should use a 10 mg/kg per dose of 3TC oral solution or a weight-based dose of 3TC tablets (neither exceeding 3TC 300 mg) as part of a once-daily regimen.<sup>23</sup> More long-term clinical trials with viral efficacy endpoints are needed to confirm that once-daily dosing of 3TC can be used effectively as part of an initial ARV regimen in children.

3TC undergoes intracellular metabolism to reach its active form, 3TC triphosphate. In adolescents, the mean half-life of intracellular 3TC triphosphate (17.7 hours) is considerably longer than that of unphosphorylated 3TC in plasma (1.5–2 hours). Intracellular concentrations of 3TC triphosphate are equivalent whether 3TC is given once daily or twice daily in adults and adolescents. This supports a recommendation for once-daily 3TC dosing based on FDA recommendations.<sup>24,25</sup>

### Considerations for Use

Weight-band dosing recommendations for 3TC have been developed for children weighing  $\geq 3$  kg and receiving either the 10 mg/mL oral solution or the 150-mg scored tablets.<sup>26-28</sup>

Both FTC and 3TC have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, see the [Hepatitis B Virus](#) section in the [Pediatric Opportunistic Infection Guidelines](#).

## References

1. Anderson PL, Lamba J, Aquilante CL, Schuetz E, Fletcher CV. Pharmacogenetic characteristics of indinavir, zidovudine, and lamivudine therapy in HIV-infected adults: a pilot study. *J Acquir Immune Defic Syndr*. 2006;42(4):441-449. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16791115>.
2. Rokx C, Gras L, van de Vijver D, Verbon A, Rijnders B, Athena National Observational Cohort Study. Virological responses to lamivudine or emtricitabine when combined with tenofovir and a protease inhibitor in treatment-naïve HIV-1-infected patients in the Dutch AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. *HIV Med*. 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26842457>.
3. Yang WL, Kouyos RD, Scherrer AU, et al. Assessing efficacy of different nucleos(t)ide backbones in NNRTI-containing regimens in the Swiss HIV Cohort Study. *J Antimicrob Chemother*. 2015;70(12):3323-3331. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26362944>.
4. Bergshoeff A, Burger D, Verweij C, et al. Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in HIV-1-infected children (PENTA-13). *Antivir Ther*. 2005;10(2):239-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15865218>.
5. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24(9):793-800. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16148846>.
6. Chaix ML, Rouet F, Kouakoussui KA, et al. Genotypic human immunodeficiency virus type 1 drug resistance in highly active antiretroviral therapy-treated children in Abidjan, Cote d'Ivoire. *Pediatr Infect Dis J*. 2005;24(12):1072-1076. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16371868>.
7. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
8. LePrevost M, Green H, Flynn J, et al. Adherence and acceptability of once daily lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J*. 2006;25(6):533-537. Available at: <http://www>.

[ncbi.nlm.nih.gov/pubmed/16732152](http://ncbi.nlm.nih.gov/pubmed/16732152).

9. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr*. 2005;39(2):189-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15905735>.
10. Mueller BU, Lewis LL, Yuen GJ, et al. Serum and cerebrospinal fluid pharmacokinetics of intravenous and oral lamivudine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother*. 1998;42(12):3187-3192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9835513>.
11. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS clinical trials group 338 study team. *JAMA*. 2000;283(4):492-498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10659875>.
12. Scherpbier HJ, Bekker V, van Leth F, Jurriaans S, Lange JM, Kuijpers TW. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics*. 2006;117(3):e528-536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16481448>.
13. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS*. 2007;21(8):947-955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17457088>.
14. Tremoulet AH, Capparelli EV, Patel P, et al. Population pharmacokinetics of lamivudine in human immunodeficiency virus-exposed and -infected infants. *Antimicrob Agents Chemother*. 2007;51(12):4297-4302. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17893155>.
15. Tremoulet AH, Nikanjam M, Cressey TR, et al. Developmental pharmacokinetic changes of lamivudine in infants and children. *J Clin Pharmacol*. 2012;52(12):1824-1832. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22180560>.
16. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nelfinavir and lamivudine pharmacokinetics during the first two weeks of life. *Pediatr Infect Dis J*. 2011;30(9):769-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21666540>.
17. Choi SY, Li F, Florian J, Seo SK. Lamivudine and abacavir clinical summary review. 2014. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM446104.pdf>.
18. Adkison K, McCoig C, Wolstenholme A, et al. Effect of sorbitol on lamivudine pharmacokinetics following administration of EPIVIR® solution in adults. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
19. Bouazza N, Hirt D, Blanche S, et al. Developmental pharmacokinetics of lamivudine in 580 pediatric patients ranging from neonates to adolescents. *Antimicrob Agents Chemother*. 2011;55(7):3498-3504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21576443>.
20. Paediatric European Network for Treatment of AIDS. Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-<36 months. *Antivir Ther*. 2010;15(3):297-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20516550>.
21. Musiime V, Kendall L, Bakeera-Kitaka S, et al. Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. *Antivir Ther*. 2010;15(8):1115-1124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21149918>.
22. Musiime V, Kasirye P, Naidoo-James B, et al. Once vs. twice-daily abacavir and lamivudine in African children. *AIDS*. 2016;30(11):1761-70 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27064996>.
23. Janssen EJH, Bastiaans DET, Valitalo PAJ, et al. Dose evaluation of lamivudine in human immunodeficiency virus-infected children aged 5 months to 18 years based on a population pharmacokinetic analysis. *Br J Clin Pharmacol*. 2017;83(6):1287-1297. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28079918>.
24. Yuen GJ, Lou Y, Bumgarner NF, et al. Equivalent steady-state pharmacokinetics of lamivudine in plasma and lamivudine triphosphate within cells following administration of lamivudine at 300 milligrams once daily and 150 milligrams twice daily. *Antimicrob Agents Chemother*. 2004;48(1):176-182. Available at: <http://www.ncbi.nlm.nih.gov/>

[pubmed/14693537](https://pubmed.ncbi.nlm.nih.gov/pubmed/14693537).

25. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17664328>.
26. World Health Organization. Preferred antiretroviral medicines for treating and preventing HIV infection in younger children: report of the WHO paediatric antiretroviral working group. 2008. Available at: [https://www.who.int/hiv/paediatric/Sum\\_WHO\\_ARV\\_Ped\\_ARV\\_dosing.pdf](https://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf).
27. L'Homme R F, Kabamba D, Ewings FM, et al. Nevirapine, stavudine and lamivudine pharmacokinetics in African children on paediatric fixed-dose combination tablets. *AIDS.* 2008;22(5):557-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316996>.
28. World Health Organization. Dosages of ARV drugs for adults and adolescents. 2018. Available at: [https://www.who.int/hiv/pub/guidelines/ARV\\_Guidelines-2018-Annex3.pdf?ua=1](https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1).

# Tenofovir Alafenamide (TAF, Vemlidy) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

Tablets: 25 mg<sup>a</sup>

### Fixed-Dose Combination Tablets:

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

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

## Dosing Recommendations

### [Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (TAF)

*Child (Weighing <25 kg) Dose:*

- There are no data on the appropriate dose of Biktarvy in children weighing <25 kg. [Studies are currently being conducted to identify the appropriate dose for this age and weight group.](#)

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

- [One tablet once daily with or without food in antiretroviral therapy \(ART\)-naïve 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 mutations 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

## Selected Adverse Events

- Asthenia, headache, diarrhea, nausea
- Increased serum lipids

## Special Instructions

- Measure serum creatinine before starting a TAF-containing regimen.
- Screen patients for hepatitis B virus (HBV) infection before initiating TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TAF.
- The Food and Drug Administration (FDA) does not recommend using Genvoya with other ARV drugs, but this FDC tablet has safely been used with darunavir (DRV).<sup>1</sup> Descovy can be safely used with DRV or atazanavir in patients weighing ≥35 kg.<sup>2</sup>
- **Do not use** Genvoya with elvitegravir, COBI, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs that are coformulated with COBI.
- When using Odefsey, patients must be able to take it with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal) because it contains rilpivirine.

## Metabolism/Elimination

### TAF Dosing in Patients with Hepatic Impairment:

- TAF-containing formulations do not require dose adjustment in patients with mild or

transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but **not** a boosted PI).

**Body Weight  $\geq 35$  kg:**

- One tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

**[Genvoya] Elvitegravir/Cobicistat/Emtricitabine/TAF**

*Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:*

- One tablet once daily with food in ART-naïve 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 mutations associated with resistance to the individual components of Genvoya.

**[Odefsey] Emtricitabine/Rilpivirine/TAF**

*Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily with a meal in ART-naïve patients with HIV RNA  $\leq 100,000$  copies/mL. This dose of Odefsey 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 mutations associated with resistance to the individual components of Odefsey.

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

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet once daily with food in ART-naïve patients. This dose of Symtuza 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 mutations associated with resistance to the individual components of Symtuza.

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:**

- TAF is renally excreted.
- No dose adjustment of the TAF 25-mg tablet (Vemlidy)<sup>a</sup> is required in patients with estimated creatinine clearance (CrCl)  $\geq 15$  mL/min, or in patients with estimated CrCl  $< 15$  mL/min (i.e., end stage renal disease) who are receiving chronic hemodialysis. See the Vemlidy product label for information on the use of the TAF 25 mg tablet in patients with estimated CrCl  $\leq 15$  mL/min.<sup>3</sup>
- TAF-containing coformulations **are not recommended** for use in patients with estimated CrCl  $< 30$  mL/min.

<sup>a</sup> TAF 25-mg tablets (Vemlidy) are approved by the FDA for treatment of HBV. In certain circumstances, TAF 25 mg tablets (Vemlidy) might be used as one component of a combination ARV regimen, with dosing recommendations similar to those for Descovy.

**Drug Interactions** (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.<sup>2</sup> 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 (RPV) and dolutegravir (DTG) did not change either TAF or TFV exposure. Coadministration of TAF with the P-gp and BCRP inhibitor cobicistat (COBI), or coadministration with atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r), increased both TAF and TFV exposures. Coadministration of TAF with darunavir/ritonavir (DRV/r) resulted in unchanged TAF area under the curve (AUC) and a doubling of TFV AUC. Coadministration of TAF with the P-gp and BCRP inducer efavirenz decreased TAF and TFV exposures.<sup>4</sup>

- Coadministration of TAF with rifamycins (**rifabutin, rifampin, or rifapentine**) **is not recommended**.<sup>3,5</sup>
- Genvoya contains **elvitegravir** (EVG) and **COBI** in addition to TAF. EVG is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by uridine diphosphate glucuronosyltransferase 1A1/3, and by oxidative metabolism pathways. EVG is a modest inducer of CYP2C9. COBI is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, COBI inhibits the adenosine triphosphate-dependent transporters BCRP and P-gp and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions when using both EVG and COBI.
- *Absorption:* Administering EVG and bictegravir (BIC) concurrently with antacids 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 (e.g., calcium, iron) decreases absorption of integrase strand transfer inhibitors (INSTIs), including EVG and BIC. Because of this, Genvoya or Biktarvy should be administered at least 4 hours before or after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium. The Food and Drug Administration (FDA) product label should be consulted for exact recommendations on the timing of dosing for each drug.
- Odefsey contains RPV, which is a CYP3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.
- Before Genvoya, Odefsey, Descovy, Biktarvy, or Symtuza is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion (e.g., acyclovir, ganciclovir, high-dose nonsteroidal anti-inflammatory drugs) could reduce clearance of TAF or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Genvoya.
- *Protease inhibitors:* Genvoya should not be administered concurrently with products or regimens that contain ritonavir (RTV), because COBI and RTV have similar effects on CYP3A metabolism.

### **Major Toxicities**

- *More common:* Nausea, diarrhea, headache. **Greater weight gain has been reported with the use of TAF than with TDF.**<sup>6,7</sup>
- *Less common (more severe):* Cases of lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors (NRTIs).

### **Resistance**

The International Antiviral Society-USA (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

TAF is available as a component of several fixed-dose combination (FDC) tablets. These FDC tablets are listed in [Appendix A, Table 1](#) and [Table 2](#).

Descovy, an FDC tablet that contains FTC and TAF (FTC/TAF), is approved by the FDA for use in children aged  $\geq 6$  years who weigh  $\geq 25$  kg (but  $< 35$  kg) when used as part of an ARV regimen that does not include a boosted protease inhibitor (PI). Descovy is approved by the FDA for use in children aged  $\geq 6$  years who weigh  $\geq 35$  kg when used in combination with any ARV drugs, including RTV-boosted or COBI-boosted PIs. Odefsey, an FDC tablet that contains FTC, RPV, and TAF (FTC/RPV/TAF), is approved by the FDA for use in children who weigh  $\geq 35$  kg.<sup>8</sup> Genvoya, an FDC tablet that contains EVG, COBI, FTC, and TAF (EVG/c/FTC/TAF), is approved by the FDA for use in children aged  $\geq 6$  years who weigh  $\geq 25$  kg when used as the single-tablet regimen (STR) without other ARV drugs (see Table A).<sup>9</sup> BIC is only available as part of the FDC tablet Biktarvy, which contains BIC, FTC, and TAF (BIC/FTC/TAF). Biktarvy is approved by the FDA for use in children or adolescents who weigh  $\geq 25$  kg.<sup>10,11</sup> Symtuza, an FDC tablet that contains DRV, COBI, FTC, and TAF (DRV/c/FTC/TAF) is approved by the FDA for use in **children and adolescents who weigh  $\geq 40$  kg.**<sup>12</sup>

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  $\geq 8$  years, but 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 (see [Appendix A, Table 2](#)). EVG/c/FTC/TAF contains TAF 10 mg while FTC/TAF, FTC/RPV/TAF, and BIC/FTC/TAF contain TAF 25 mg. COBI boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, administration of EVG/c/FTC/TAF, which contains TAF 10 mg and COBI, achieves TFV-DP systemic exposure that is similar to the exposure achieved by FTC/RPV/TAF or BIC/FTC/TAF, which contain TAF 25 mg but no COBI.

**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	N/A	25 kg	Use with an INSTI or NNRTI, but <b>not</b> with a boosted PI.
	FTC/TAF	25 mg	N/A	35 kg	Use with any ARV drugs, including a boosted PI.
Odefsey	FTC/RPV/TAF	25 mg	12 years	35 kg	<b>Generally not to be used with other ARV drugs.</b> <sup>a</sup>
Genvoya	EVG/c/FTC/TAF	10 mg	N/A	25 kg	TAF dose is lower because of the COBI boosting. <b>Generally not to be used with other ARV drugs.</b> <sup>a</sup>
Biktarvy	BIC/FTC/TAF	25 mg	N/A	25 kg	<b>Generally not to be used with other ARV drugs.</b> <sup>a</sup>

<sup>a</sup> Consult a specialist in HIV care before using these FDC tablets with other ARV agents.

**Key:** ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; 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<sup>13,14</sup> 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).<sup>15</sup> 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<sup>16</sup> also has good oral bioavailability.<sup>17</sup> 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.<sup>18</sup> Once inside the cell, TAF is hydrolyzed to TFV,<sup>19,20</sup> 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.<sup>16</sup> 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.<sup>18,21</sup> Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy that is equivalent to the antiviral efficacy of TDF. However, the toxicities that are specifically related to high plasma TFV concentrations should not occur when using TAF. High plasma TFV concentration has been linked to TDF-related endocrine disruption that is associated with low bone mineral density (BMD).<sup>22</sup> High plasma TFV has also been closely associated with both glomerular<sup>22-24</sup> and proximal tubular<sup>25</sup> renal toxicity.

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

Parameter	TAF 8 mg (n = 9)	TDF 300 mg (n = 6)
Plasma TFV AUC <sub>tau</sub> (ng·h/mL)	65.5 (23.5)	1,918.0 (39.4)
Plasma TFV C <sub>max</sub> (ng/mL)	4.2 (24.7)	252.1 (36.6)
Plasma TFV C <sub>tau</sub> (ng/mL)	2.1 (33.8)	38.7 (44.7)
PBMC TFV-DP AUC <sub>tau</sub> (µM·h)	3.5 (77.1)	3.0 (119.6)

**Note:** The mean age of participants was 38 years, with a range of 20 to 57 years. Data are mean (% coefficient of variation), tau is the dosing interval (i.e., 24 hours), and C<sub>max</sub> is the maximum concentration.

**Source:** Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr*. 2013;63(4):449-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23807155>.

**Key:** AUC = area under the curve; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir; TFV-DP = tenofovir diphosphate

## Tenofovir Alafenamide Efficacy in Clinical Trials in Adults

In adults, TAF is noninferior to TDF in its ability to control viral load over 48 to 96 weeks when used in combination with EVG, COBI, and FTC;<sup>26-29</sup> with FTC and RPV;<sup>30</sup> with DRV, COBI, and FTC;<sup>31-33</sup> and when TAF and FTC are administered in combination with other ARV drugs.<sup>34</sup> In a switch study of adults who were virologically suppressed on a three-drug regimen that included abacavir (ABC), FTC/TAF was noninferior to a regimen of lamivudine plus ABC plus a third ARV drug over 48 weeks. 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 ABC group had an increase in HDL cholesterol levels (-2 mg/dL vs. +2 mg/dL, respectively; *P* = 0.0003).<sup>35</sup> Viral load suppression was attained in about 90% of study participants when TAF was given as part of the coformulated STR BIC/FTC/TAF.<sup>36-38</sup>

## Tenofovir Alafenamide Efficacy in Clinical Trials in Adolescents and Children

The combination of TAF, EVG, COBI, and FTC has been shown to have similar efficacy when used in adults and two groups of children: those aged  $\geq 12$  years and weighing  $\geq 35$  kg<sup>39</sup> and those aged  $\geq 6$  years and weighing  $\geq 25$  kg.<sup>40</sup> In one study, treatment with the STR BIC/FTC/TAF resulted in viral load suppression in 100% of 24 children aged 12 years to <18 years.<sup>10</sup>

### Pharmacokinetics

#### Drug Exposure and Virologic Response

Virologic suppression in people who are taking TAF or TDF is most closely related to intracellular TFV-DP concentrations. At clinically meaningful doses, TAF generates peripheral blood mononuclear cell TFV-DP concentrations in adults that are two-fold<sup>21</sup> to seven-fold higher than those generated with TDF.<sup>18,26</sup> Higher TFV-DP concentrations result in a stronger antiviral potency<sup>18</sup> and a higher barrier to resistance.<sup>41,42</sup>

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 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.<sup>39</sup>

#### Drug Exposure and Safety: All Age Groups

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

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

**Table C. Plasma Tenofovir Alafenamide and Plasma Tenofovir Exposures When Tenofovir Alafenamide and Tenofovir Disoproxil Fumarate are Used with Boosted Antiretroviral Drugs**

Regimen	TAF AUC <sup>a</sup>	TAF AUC Ratio TAF AUC of TAF-Containing Regimen/TAF AUC of Genvoya (Adult Exposure)	TFV AUC <sup>a</sup>	TFV AUC Ratio TFV AUC of TAF-Containing Regimen/TFV AUC of Stribild (Adult Exposure)
<b>Adult</b>				
Stribild (EVG/c/FTC/TDF 300 mg)	N/A	N/A	4,400	1.00
Genvoya (EVG/c/FTC/TAF 10 mg)	210	1.0	290	0.07
DRV/r plus TAF 25 mg <sup>b</sup>	196	0.93	259	0.06
DRV/c plus TAF 25 mg	239	1.1	935	0.21
<b>Pediatric</b>				
Stribild (EVG/c/FTC/TDF 300 mg) for ages 12–18 years	N/A	N/A	6,028	1.37
Genvoya (EVG/c/FTC/TAF 10 mg) for ages 12–18 years	200	0.95	290	0.07
Genvoya (EVG/c/FTC/TAF 10 mg) for ages 6–12 years	330	1.6	440	0.10

<sup>a</sup> AUC: ng·h/mL

<sup>b</sup> 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:** AUC = area under the curve; DRV/r = darunavir/ritonavir; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FTC = emtricitabine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV = tenofovir

The clinical trials in adults that have shown the safety of FTC plus TAF administered with ATV/r or DRV/r have used FTC/TAF 200 mg/10 mg, a formulation that is not available in the United States.<sup>43</sup> The FDA states that when FTC/TAF 200 mg/25 mg is combined with boosted ATV, DRV, or LPV 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).<sup>2</sup> 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 than in the TDF arm.<sup>44</sup> Hence, FTC/TAF 25 mg was recommended for approval instead of FTC/TAF 10 mg.<sup>44</sup> This is not the case in Canada or Europe, where FTC is combined with TAF 10 mg in an FDC for use in combination with boosted PIs.

*Drug Exposure and Safety: Aged 12 to 18 Years and Weighing  $\geq 35$  kg*

A study of FTC/TAF in 18 children and adolescents (aged 12 to 18 years and weighing  $\geq 35$  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%).<sup>45</sup>

Studies of EVG/c/FTC/TAF in children aged 12 to 18 years and weighing  $\geq 35$  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.<sup>39</sup> 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).<sup>2</sup>

The adult-dose formulation of Biktarvy (which contains BIC 50 mg/FTC 200 mg/TAF 25 mg) was administered to youth aged 12 years to  $<18$  years and weighing  $\geq 35$  kg 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.<sup>10</sup> While the AUC and  $C_{\max}$  for BIC were similar in adolescents and adults, the mean BIC trough concentration in adolescents aged 12 years to  $<18$  years was 2,327 ng/mL (with a CV of 49%); in adults, the mean BIC trough concentration was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% confidence interval, 74% to 100%).<sup>10</sup>

BIC 50 mg/FTC 200 mg/TAF 25 mg was administered to children aged 6 years to  $<12$  years who weighed  $\geq 25$  kg and who had had viral loads  $<50$  copies/mL for  $\geq 6$  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 (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. 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.<sup>46</sup>

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

Studies of EVG/c/FTC/TAF in children aged 6 years to  $<12$  years who weighed  $\geq 25$  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.<sup>40,47</sup> This led to FDA approval of EVG/c/FTC/TAF for use in children aged  $\geq 6$  years and weighing  $\geq 25$  kg.<sup>9</sup> **Follow-up to 96 weeks in a small number of participants showed no change from baseline in the median spine BMD z-score, but there was a decline in the median total body BMD z-score and a possible decline in median eGFR.**<sup>48</sup>

Because INSTIs do not increase TAF concentrations, regimens that include FTC/TAF 25 mg plus an INSTI are expected to result in safe drug exposures that are similar to those seen with the STR EVG/c/FTC/TAF 10 mg. This led the FDA to approve FTC/TAF 25 mg for use in children aged  $\geq 6$  years and weighing  $\geq 25$  kg when used in combination with other ARV drugs that do not include a boosted PI.<sup>2</sup>

Because boosted ATV, DRV, or LPV increase TAF exposure to concentrations that are higher than those seen with use of EVG/c/FTC/TAF, and because there are no data on the use of this combination in children weighing <35 kg, the safety of FTC/TAF combined with COBI-boosted or RTV-boosted PIs in children weighing between 25 kg and <35 kg cannot be assured. That is why the FDA approval for FTC/TAF used in combination with boosted PIs is limited to children weighing  $\geq 35$  kg (see Table A).<sup>2</sup>

#### *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 DTG tablets. The crushed tablets were mixed with water and administered via a gastrostomy tube. Each dose was followed by a can of a nutritional supplement. No PK parameters were measured.<sup>49</sup> **In adults without HIV, the PKs of crushed DRV/c/FTC/TAF tablets showed decreased TAF bioavailability compared to whole tablets. The clinical implications of these findings are unclear.**<sup>50</sup>

#### **Toxicity**

##### *Bone*

TAF causes bone toxicity less frequently than TDF.<sup>26-28,31-34,51,52</sup> For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/c/FTC/TAF had a smaller decrease in BMD at the spine (mean change -1.30% vs. -2.86%;  $P < 0.0001$ ) and hip (-0.66% vs. -2.95%;  $P < 0.0001$ ) at 48 weeks than those given EVG/c/FTC/TDF.<sup>26</sup> These differences were maintained to 96 weeks.<sup>29</sup> **The clinical importance of these changes in BMD are unclear.**

##### *Renal*

Studies in adolescents aged 12 to 17 years<sup>39</sup> and adults<sup>26-28,31,32,34</sup> show that TAF is less frequently associated with glomerular and renal tubular damage than TDF.<sup>53</sup> For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/c/FTC/TAF had a smaller mean increase in serum creatinine (0.08 mg/dL vs. 0.12 mg/dL;  $P < 0.0001$ ) than those given EVC/c/FTC/TDF, and a smaller percent change from baseline in urine protein to creatinine ratio (median % change -3% vs. +20%;  $P < 0.0001$ ) at 48 weeks.<sup>26</sup> These differences persisted to 96 weeks of follow-up.<sup>29</sup> Safety of EVG/c/FTC/TAF has been demonstrated in adults with estimated creatinine clearances between 30 mL/min and 69 mL/min.<sup>54</sup> TAF may require less intense renal safety monitoring than TDF, but more experience with the drug in broad clinical practice will be needed before a specific recommendation can be made.

##### *Lipids*

In treatment-naïve adults who were evaluated after 48 weeks of therapy, initiation of EVG/c/FTC/TAF was associated with increases in serum lipids that were greater than those observed with the initiation of EVG/c/FTC/TDF, with a mean increase in total cholesterol levels of 31 mg/dL versus 23 mg/dL and a mean increase in LDL cholesterol levels of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents who were treated with EVG/c/FTC/TAF, the following median changes from baseline occurred at Weeks 24 and 36: fasting total cholesterol levels increased 26 mg/dL and 36 mg/dL, respectively; fasting direct LDL levels increased 10 mg/dL and 17 mg/dL, respectively; and fasting triglycerides increased 14 mg/dL and 19 mg/dL, respectively.<sup>55</sup> 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.<sup>32</sup> Monitoring serum lipids while the patient is taking TAF-containing FDC tablets is warranted, given these data. For more information, see [Table 15b](#).

## **References**

1. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193-200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27753684>.
2. Emtricitabine and tenofovir alafenamide (Descovy) [package insert]. Food and Drug Administration. 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/208215s001lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208215s001lbl.pdf).

3. Tenofovir alafenamide (Vemlidy) [package insert]. Food and Drug Administration. 2020. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/208464s008lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208464s008lbl.pdf).
4. Begley R, Das M, Zhong L, Ling J, Kearney BP, Custodio JM. Pharmacokinetics of tenofovir alafenamide when coadministered with other HIV antiretrovirals. *J Acquir Immune Defic Syndr*. 2018;78(4):465-472. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29649076>.
5. Cerrone M, Alfarisi O, Neary M, et al. Rifampin effect on tenofovir alafenamide (TAF) plasma/intracellular pharmacokinetics. Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/rifampin-effect-tenofovir-alafenamide-taf-plasmaintracellular-pharmacokinetics>.
6. Gomez M, Seybold U, Roeder J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017. *Infection*. 2019;47(1):95-102. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30269210>.
7. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med*. 2019;381(9):803-815. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31339677>.
8. Emtricitabine/rilpivirine/tenofovir alafenamide (Odefsey) [package insert]. Food and Drug Administration. 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/208351s001lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208351s001lbl.pdf).
9. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/207561s020lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207561s020lbl.pdf).
10. Gaur A, Rodriguez C, McGrath EJ, et al. Bictegravir/FTC/TAF single-tablet regimen in adolescents: week 24 results. Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/bictegravirftctaf-single-tablet-regimen-adolescents-week-24-results>.
11. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/210251s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210251s006lbl.pdf).
12. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza) [package insert]. Food and Drug Administration. 2020. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/210455s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210455s009lbl.pdf).
13. Barditch-Crovo P, Deeks SG, Collier A, et al. Phase i/ii trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother*. 2001;45(10):2733-2739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11557462>.
14. Tong L, Phan TK, Robinson KL, et al. Effects of human immunodeficiency virus protease inhibitors on the intestinal absorption of tenofovir disoproxil fumarate in vitro. *Antimicrob Agents Chemother*. 2007;51(10):3498-3504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17664327>.
15. Lee WA, Martin JC. Perspectives on the development of acyclic nucleotide analogs as antiviral drugs. *Antiviral Res*. 2006;71(2-3):254-259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16837073>.
16. Lee WA, He GX, Eisenberg E, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. *Antimicrob Agents Chemother*. 2005;49(5):1898-1906. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15855512>.
17. Babusis D, Phan TK, Lee WA, Watkins WJ, Ray AS. Mechanism for effective lymphoid cell and tissue loading following oral administration of nucleotide prodrug GS-7340. *Mol Pharm*. 2013;10(2):459-466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22738467>.
18. 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>.
19. Birkus G, Kutty N, He GX, et al. Activation of 9-[(R)-2-[[[(S)-1-(Isopropoxycarbonyl)ethyl]amino]phenoxyphosphinyl]-methoxy]propyl]adenine (GS-7340) and other tenofovir phosphonoamidate prodrugs by human proteases. *Mol Pharmacol*. 2008;74(1):92-100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18430788>.

20. Birkus G, Wang R, Liu X, et al. Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. *Antimicrob Agents Chemother*. 2007;51(2):543-550. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17145787>.
21. Podany AT, Bares SH, Havens J, et al. Plasma and intracellular pharmacokinetics of tenofovir in patients switched from tenofovir disoproxil fumarate to tenofovir alafenamide. *AIDS*. 2018;32(6):761-765. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29334548>.
22. Havens PL, Kiser JJ, Stephensen CB, et al. Association of higher plasma vitamin D binding protein and lower free calcitriol levels with tenofovir disoproxil fumarate use and plasma and intracellular tenofovir pharmacokinetics: cause of a functional vitamin D deficiency? *Antimicrob Agents Chemother*. 2013;57(11):5619-5628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24002093>.
23. Poizot-Martin I, Solas C, Allemand J, et al. Renal impairment in patients receiving a tenofovir-cART regimen: impact of tenofovir trough concentration. *J Acquir Immune Defic Syndr*. 2013;62(4):375-380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23196828>.
24. Baxi SM, Scherzer R, Greenblatt RM, et al. Higher tenofovir exposure is associated with longitudinal declines in kidney function in women living with HIV. *AIDS*. 2016;30(4):609-618. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26558723>.
25. Rodriguez-Novoa S, Labarga P, D'Avolio A, et al. Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations. *AIDS*. 2010;24(7):1064-1066. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20299966>.
26. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25890673>.
27. Sax PE, Zolopa A, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized Phase 2 study. *J Acquir Immune Defic Syndr*. 2014;67(1):52-58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24872136>.
28. Mills A, Garner W, Pozniak A, et al. Patient-reported symptoms over 48 weeks in a randomized, open-label, Phase IIIb non-inferiority trial of adults with HIV switching to co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir DF versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir DF. *Patient*. 2015;8(4):359-371. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26045359>.
29. Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *J Acquir Immune Defic Syndr*. 2016;72(1):58-64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26829661>.
30. Orkin C, DeJesus E, Ramgopal M, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, Phase 3b, non-inferiority study. *Lancet HIV*. 2017;4(5):e195-e204. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28259777>.
31. Mills A, Crofoot G Jr, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized Phase 2 study. *J Acquir Immune Defic Syndr*. 2015;69(4):439-445. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25867913>.
32. Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized Phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. *AIDS*. 2018;32(11):1431-1442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29683855>.
33. Orkin C, Molina JM, Negredo E, et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a Phase 3, randomised, non-inferiority trial. *Lancet HIV*. 2018;5(1):e23-e34. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28993180>.
34. Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil

fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled Phase 3 trial. *Lancet HIV*. 2016;3(4):e158-165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27036991>.

35. Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority Phase 3 trial. *Lancet HIV*. 2018;5(4):e162-e171. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29475804>.
36. Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, Phase 3, non-inferiority trial. *Lancet*. 2017;390(10107):2073-2082. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28867499>.
37. Sax PE, DeJesus E, Crofoot G, et al. Bictegravir versus dolutegravir, each with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, Phase 2 trial. *Lancet HIV*. 2017;4(4):e154-e160. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28219610>.
38. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, Phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017;390(10107):2063-2072. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28867497>.
39. Gaur AH, Kizito H, Prasitsueubsai W, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. *Lancet HIV*. 2016;3(12):e561-e568. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27765666>.
40. Natukunda E, Gaur A, Kosalaraksa P, et al. Safety, efficacy, and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial. *Lancet Child Adolescent Health*. 2017;1(1):27-34. Available at: <http://www.sciencedirect.com/science/article/pii/S2352464217300093?via%3Dihub>.
41. Margot NA, Liu Y, Miller MD, Callebaut C. High resistance barrier to tenofovir alafenamide is driven by higher loading of tenofovir diphosphate into target cells compared to tenofovir disoproxil fumarate. *Antiviral Res*. 2016;132:50-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27208653>.
42. Margot NA, Wong P, Kulkarni R, et al. Commonly transmitted HIV-1 drug resistance mutations in reverse-transcriptase and protease in antiretroviral treatment-naive patients and response to regimens containing tenofovir disoproxil fumarate or tenofovir alafenamide. *J Infect Dis*. 2017;215(6):920-927. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28453836>.
43. Post FA, Yazdanpanah Y, Schembri G, et al. Efficacy and safety of emtricitabine/tenofovir alafenamide (FTC/TAF) vs. emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a backbone for treatment of HIV-1 infection in virologically suppressed adults: subgroup analysis by third agent of a randomized, double-blind, active-controlled Phase 3 trial. *HIV Clin Trials*. 2017;18(3):135-140. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28303753>.
44. Food and Drug Administration. Descovy medical review. 2015. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/208215Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000MedR.pdf).
45. Chen J, Saez-Llorens X, Castano E, et al. Safety, pharmacokinetics, and efficacy of FTC/TAF in HIV-infected adolescents (12–18 years). Abstract #843. Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/safety-pk-efficacy-ftctaf-hiv-infected-adolescents-12-18-yrs>.
46. Cotton M, Liberty A, Rodriguez CA, et al. Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in HIV-1-infected children (6 to < 12 years). International AIDS Conference July. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_39.htm](http://www.natap.org/2018/IAC/IAC_39.htm).
47. Foca M. Fixed-dose combination therapy for paediatric HIV infection. *Lancet*. 2017;1(1):3-4. Available at: [http://www.theLancet.com/journals/lanchi/article/PIIS2352-4642\(17\)30015-9/fulltext](http://www.theLancet.com/journals/lanchi/article/PIIS2352-4642(17)30015-9/fulltext).

48. Rakhmanina N, Natukunda E, Kosalaraksa P, Batra J, Gaur A, et al. Safety and efficacy of E/C/F/TAF in virologically suppressed, HIV-infected children through 96 weeks. Abstract 22. 11th International Workshop on HIV Pediatrics. 2019. Mexico City, Mexico.
49. Fulco PP, Higginson RT. Enhanced HIV viral load suppression with crushed combination tablets containing tenofovir alafenamide and emtricitabine. *Am J Health Syst Pharm*. 2018;75(10):594-595. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29748295>.
50. Brown K, Thomas D, McKenney K, et al. Impact of splitting or crushing on the relative bioavailability of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen. *Clin Pharmacol Drug Dev*. 2019;8(4):541-548. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30508308>.
51. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, Phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16(1):43-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26538525>.
52. DeJesus E, Haas B, Segal-Maurer S, et al. Superior efficacy and improved renal and bone safety after switching from a tenofovir disoproxil fumarate- to a tenofovir alafenamide-based regimen through 96 weeks of treatment. *AIDS Res Hum Retroviruses*. 2018;34(4):337-342. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29368537>.
53. Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate: A pooled analysis of 26 clinical trials. *AIDS*. 2019;33(9):1455–1465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30932951>.
54. Pozniak A, Arribas JR, Gathe J, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label Phase 3 study. *J Acquir Immune Defic Syndr*. 2016;71(5):530-537. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26627107>.
55. Tauber WB, Lewis LL. Clinical review of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (genvoya). 2015. Available at: <http://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm478088.pdf>.

## Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

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

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

#### Fixed-Dose Combination Tablets

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

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Neonate and Infant Dose:

- Tenofovir disoproxil fumarate (TDF) has not been approved by the Food and Drug Administration or recommended for use in neonates and infants aged <2 years.

#### Child (Aged $\geq 2$ Years to <12 Years) Dose:<sup>a</sup>

- TDF 8 mg/kg per dose once daily

### Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Glomerular and proximal renal tubular dysfunction
- Decreased bone mineral density<sup>a</sup>

### Special Instructions

- TDF oral powder formulation is available for patients who are unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: one level scoop = 1 g powder = TDF 40 mg.
- Mix TDF oral powder with 2 to 4 oz. of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with

### 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)

### 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)<sup>a</sup> 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 antiretroviral therapy (ART)-naïve adults with baseline HIV RNA ≤100,000 copies/mL. This dose of Complera can also be used in virologically suppressed (HIV RNA <50 copies/mL) adults who are currently on their first or second regimen and who have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.

liquid. The powder may float on the top even after vigorous stirring.

- Although TDF can be administered without regard to food, food requirements vary depending on the other ARV drugs contained in an 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 during continued therapy (see [Table 15i](#)). Measure serum phosphate if there is clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before using TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, hepatic function should be monitored for several months after patients with HBV infection stop taking TDF.
- Tenofovir alafenamide (TAF) is associated with less bone and renal toxicity than TDF, but it has equal antiviral efficacy. **Do not use TAF and TDF together.** Consider switching from TDF to TAF in appropriate clinical settings.

### Metabolism/Elimination

#### TDF Dosing in Patients with Renal Insufficiency:

- TDF is renally excreted.
- The dose of TDF should be decreased in patients with impaired renal function (creatinine clearance [CrCl] <50 mL/min). Consult the manufacturer's prescribing information for directions on how to adjust the dose in accordance with CrCl.
- The FDCs Atripla, Complera, and Symfi Lo should not be used in patients with CrCl <50 mL/min or in patients who require dialysis.
- The FDC Truvada should not be used in patients with CrCl <30 mL/min or in patients who require dialysis.
- The FDC Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

- Administer with a meal of  $\geq 500$  calories.

#### **[Delstrigo] Doravirine/Emtricitabine/TDF**

##### *Adult Dose:*

- One tablet once daily in ART-naive adults. This dose of Delstrigo 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 with no history of treatment failure and no known mutations associated with resistance to the individual components of Delstrigo.
- Not studied in children or adolescents (see the [Doravirine](#) section for more information)

#### **[Stribild] Elvitegravir/Cobicistat/Emtricitabine/TDF**

##### *Adolescent (Weighing $> 35$ kg with a Sexual Maturity Rating [SMR] of 4 or 5) and Adult Dose:*

- One tablet once daily in ART-naive adults. This dose of Stribild 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 mutations associated with resistance to the individual components of Stribild.
- Administer with food.

#### **[Symfi] Efavirenz 600 mg/Lamivudine/TDF**

##### *Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose:*

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

#### **[Symfi Lo] Efavirenz 400 mg/Lamivudine/TDF**

##### *Child and Adolescent (Weighing $\geq 35$ kg) and Adult Dose:*

- One tablet once daily
- Take on an empty stomach.
- Symfi Lo has not been studied in children (SMR 1 to 3), and major inter-individual variability in efavirenz (EFV) plasma concentrations has been found in pediatric patients in a multi-ethnic setting. The 400-mg dose of EFV may be too low in children or adolescents with SMRs of 1 to 3 who weigh  $\geq 40$  kg. Therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients weighing  $\geq 40$  kg. See the [Efavirenz](#) section for more

information.

### [Temixys] Lamivudine/TDF

Child and Adolescent (Weighing  $\geq 35$  kg) and Adult

Dose:

- One tablet once daily

### [Truvada] Emtricitabine/TDF (FTC/TDF)

Child, Adolescent, and Adult Dose:

#### Truvada Dosing Table

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

<sup>a</sup> See text for a discussion of the concerns about decreased bone mineral density in patients who are receiving TDF, especially in prepubertal patients and those in early puberty (SMR 1 or 2).

**Drug Interactions** (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.<sup>1</sup>
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of plasma tenofovir (TFV). **Avoid frequent or long-term use of nonsteroidal anti-inflammatory drugs in patients who are taking TDF.**
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine (ddI) serum concentrations increase when this drug is coadministered with TDF, and this combination **should not be used** because of the increased risk of ddI toxicity.
- *Protease inhibitors:* Atazanavir (ATV) without ritonavir **should not be coadministered** with TDF because TDF decreases ATV plasma concentrations. In addition, the combination of ATV and lopinavir/ritonavir increases plasma TFV concentrations and increases the risk of TDF-associated toxicity.<sup>2</sup>
- *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  $\geq 2$  years when used as a component of antiretroviral therapy (ART). TDF is available as a component of FDC tablets (see [Appendix A, Table 2](#)).

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is approved by the FDA for HBV treatment in children aged  $\geq 12$  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  $\geq 12$  years and weighing  $\geq 35$  kg is TDF 300 mg once daily. For children aged 2 to 12 years, the FDA-approved dose is TDF 8 mg/kg per dose administered once daily, which closely approximates the dose of TDF 208 mg/m<sup>2</sup> per dose used in early studies in children.<sup>3</sup>

In adults, the recommended once-daily dose of TDF 300 mg is highly effective. In comparative clinical trials in adults, TDF administered with lamivudine (3TC) or emtricitabine (FTC) as a dual-NRTI backbone in combination with efavirenz (EFV) had better viral efficacy than zidovudine (ZDV) or stavudine (d4T) administered with 3TC and EFV.<sup>4-6</sup> TDF administered with FTC has been compared to abacavir (ABC) administered with 3TC in several adult studies and meta-analyses, with variable results.<sup>7-11</sup>

The FDA approved Cimduo and Temixys (both of which contain 3TC 300 mg/TDF 300 mg) and Symfi (EFV 600 mg/3TC 300 mg/TDF 300 mg) after reviewing the results of a clinical trial that compared the use of TDF to the use of d4T when each drug was administered with 3TC and EFV.<sup>5,12</sup> This trial showed that TDF and d4T had similar virologic response; however, TDF had lower toxicity than d4T.

FDA approval of Symfi Lo (EFV 400 mg/3TC 300 mg/TDF 300 mg) was based on a study that compared the use of EFV 400 mg to the use of EFV 600 mg, each administered with FTC 200 mg and TDF 300 mg, in 630 ART-naïve adults.<sup>13</sup> 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 to 18 years with susceptible virus. In children aged 2 years to  $< 12$  years, TDF 8 mg/kg per dose once daily was noninferior to twice-daily ZDV-containing ART or d4T-containing ART over 48 weeks of randomized treatment.<sup>14,15</sup> Virologic success is lower in treatment-experienced patients with extensive drug resistance.<sup>16-18</sup>

## **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.<sup>19</sup> A modeling study suggests that children and adolescents who are treated with TDF may have higher intracellular TFV-DP concentrations than adults,<sup>20</sup> even though plasma TFV concentrations are lower in children and adolescents, because renal clearance of TFV is higher in children than in adults.<sup>3,21,22</sup>

## **Formulations**

### *Special Considerations*

The taste-masked granules that make up the TDF oral powder give the vehicle (e.g., applesauce, yogurt) a gritty consistency. Once mixed with a vehicle, TDF should be administered promptly because its taste becomes bitter when it is allowed to sit for too long.

## **Toxicity**

### *Bone Toxicity*

TDF administration is associated with decreased BMD in both adults<sup>23,24</sup> and children.<sup>15,25-27</sup> When treated with TDF, younger children with sexual maturity ratings (SMRs) of 1 and 2 may be at a higher risk of decreased BMD than children with more advanced pubertal development (i.e., SMRs  $\geq 3$ ).<sup>21</sup> Discontinuation of TDF results in partial or complete recovery of BMD.<sup>25,28</sup>

In the industry-sponsored study that led to FDA approval of TDF in adolescents aged  $\geq 12$  years and weighing  $\geq 35$  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.<sup>16</sup>

TDF administration disrupts vitamin D metabolism,<sup>29,30</sup> 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.<sup>31</sup> During chronic TDF administration, youth with HIV who received vitamin D3 supplements (50,000 IU once monthly) had decreased serum parathyroid hormone levels and increased lumbar spine BMD compared to study participants who were not treated with high doses of vitamin D3.<sup>29,32</sup> 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 antiretroviral (ARV) regimen that included TDF and who received vitamin D3 2,000 IU or 4,000 IU daily.<sup>33</sup> Since this improvement in lumbar spine BMD was seen in patients with and without baseline vitamin D deficiency, some practitioners recommend vitamin D supplementation for all patients who are being treated with an ARV regimen that includes TDF.

High concentrations of the TDF metabolite plasma TFV have been associated with TDF-related endocrine disruption and low BMD.<sup>34</sup> Tenofovir alafenamide (TAF), which is associated with lower plasma TFV concentrations than TDF, has **less effect on parathyroid hormone** levels<sup>35</sup> and 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., SMRs 1 and 2). If DXA results are abnormal, consider referring the patient to a subspecialist in pediatric endocrinology or a related field.

TDF has been shown to be effective, and it can be administered once daily; however, the use of TDF has been associated with a risk of BMD loss. Because childhood and early adolescence are important periods of rapid bone accrual, and because children with perinatally acquired HIV are at risk for low peak bone mass, the Panel favors the use of ABC or TAF over TDF in children with SMRs 1 to 3.<sup>36,37</sup>

### *Renal Toxicity*

New onset renal impairment and worsening renal impairment have been reported in adults<sup>38</sup> and children<sup>39,40</sup> 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.<sup>18</sup> While TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.<sup>38,39</sup> Irreversible renal failure is quite rare, but cases have been reported.<sup>41</sup>

The main target of TDF nephrotoxicity is the renal proximal tubule.<sup>39</sup> Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.<sup>42,43</sup>

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.<sup>44</sup> The risks of TDF-associated proteinuria and chronic kidney disease increase with the duration of treatment.<sup>45,46</sup> Of 89 participants aged 2 to 12 years who received TDF in Gilead Study 352 (where participants had a median drug exposure of 104 weeks), four participants were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.<sup>14</sup>

Plasma TFV is the TDF metabolite most closely associated with both glomerular<sup>34,47</sup> and proximal tubular<sup>48</sup> toxicity. TAF, which generates lower plasma TFV concentrations than TDF, is associated with a lower risk of renal toxicity than TDF (see the [Tenofovir Alafenamide](#) section).<sup>49</sup>

### *Monitoring Potential Renal Toxicity*

Because TDF has the potential to decrease creatinine clearance and cause renal tubular dysfunction, the Panel recommends measuring serum creatinine and using a urine dipstick to check protein and glucose concentration before initiating TDF. It is unclear how often creatinine and renal tubular function (urine protein and glucose) should be monitored in asymptomatic patients. Many Panel members monitor creatinine with other blood tests every 3 to 4 months and perform urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and in the absence of proteinuria. Because nephrotoxicity increases with the duration of TDF treatment, monitoring should be continued during long-term therapy with the drug.

Because renal glomerular damage primarily increases the concentration of albumin in urine, and proximal renal tubular damage increases the concentration of low-molecular-weight proteins like beta-2 microglobulin in urine, dipstick urinalysis (which primarily measures urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measuring urine albumin and urine protein and calculating the ratio of urine albumin to urine protein can be helpful in identifying the nonalbumin proteinuria that is seen in TDF-associated nephrotoxicity.<sup>50,51</sup> 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 damage.

## References

1. Tenofovir disoproxil fumarate [package insert]. Food and Drug Administration. 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/021356s055,022577s011lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021356s055,022577s011lbl.pdf).
2. Bedimo R, Rosenblatt L, Myers J. Systematic review of renal and bone safety of the antiretroviral regimen efavirenz, emtricitabine, and tenofovir disoproxil fumarate in patients with HIV infection. *HIV Clin Trials*. 2016;17(6):246-266. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27809711>.
3. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother*. 2004;48(1):124-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14693529>.
4. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *J Acquir Immune Defic Syndr*. 2008;47(1):74-78. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971715>.

5. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292(2):191-201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15249568>.
6. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med*. 2006;354(3):251-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16421366>.
7. Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. *N Engl J Med*. 2009;361(23):2230-2240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19952143>.
8. Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir TDF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Infect Dis*. 2011;204(8):1191-1201. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21917892>.
9. Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. *AIDS*. 2009;23(12):1547-1556. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19542866>.
10. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr*. 2010;55(1):49-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20431394>.
11. Spaulding A, Rutherford GW, Siegfried N. Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naive individuals. *Cochrane Database Syst Rev*. 2010(10):CD008740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20927777>.
12. Margot NA, Lu B, Cheng A, Miller MD, Study 903 Team. Resistance development over 144 weeks in treatment-naive patients receiving tenofovir disoproxil fumarate or stavudine with lamivudine and efavirenz in Study 903. *HIV Med*. 2006;7(7):442-450. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16925730>.
13. ENCORE1 Study Group, Carey D, Puls R, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis*. 2015;15(7):793-802. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25877963>.
14. Saez-Llorens X, Castano E, Rathore M, et al. A randomized, open-label study of the safety and efficacy of switching stavudine or zidovudine to tenofovir disoproxil fumarate in HIV-1-infected children with virologic suppression. *Pediatr Infect Dis J*. 2015;34(4):376-382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25760565>.
15. Aurpibul L, Cressey TR, Sricharoenchai S, et al. Efficacy, safety and pharmacokinetics of tenofovir disoproxil fumarate in virologic-suppressed HIV-infected children using weight-band dosing. *Pediatr Infect Dis J*. 2015;34(4):392-397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25760566>.
16. Della Negra M, de Carvalho AP, de Aquino MZ, et al. A randomized study of tenofovir disoproxil fumarate in treatment-experienced HIV-1 infected adolescents. *Pediatr Infect Dis J*. 2012;31(5):469-473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22301477>.
17. Della Negra M, De Carvalho AP, De Aquino MZ, et al. Long-term efficacy and safety of tenofovir disoproxil fumarate in HIV-1-infected adolescents failing antiretroviral therapy: the final results of study GS-US-104-0321. *Pediatr Infect Dis J*. 2015;34(4):398-405. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25599284>.
18. Riordan A, Judd A, Boyd K, et al. Tenofovir use in human immunodeficiency virus-1-infected children in the United Kingdom and Ireland. *Pediatr Infect Dis J*. 2009;28(3):204-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19209091>.
19. Baheti G, Kiser JJ, Havens PL, Fletcher CV. Plasma and intracellular population pharmacokinetic analysis of tenofovir in HIV-1-infected patients. *Antimicrob Agents Chemother*. 2011;55(11):5294-5299. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21896913>.
20. Baheti G, King JR, Acosta EP, Fletcher CV. Age-related differences in plasma and intracellular tenofovir concentrations in HIV-1-infected children, adolescents and adults. *AIDS*. 2013;27(2):221-225. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22811111>.

[gov/pubmed/23032419](http://www.ncbi.nlm.nih.gov/pubmed/23032419).

21. Hazra R, Gafni RI, Maldarelli F, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy for pediatric HIV infection. *Pediatrics*. 2005;116(6):e846-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16291735>.
22. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2008;52(2):631-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025112>.
23. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis*. 2010;51(8):963-972. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20828304>.
24. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS clinical trials group A5224s, a substudy of ACTG A5202. *J Infect Dis*. 2011;203(12):1791-1801. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21606537>.
25. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics*. 2006;118(3):e711-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16923923>.
26. Purdy JB, Gafni RI, Reynolds JC, Zeichner S, Hazra R. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. *J Pediatr*. 2008;152(4):582-584. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18346519>.
27. Aurrubul L, Puthanakit T. Review of tenofovir use in HIV-infected children. *Pediatr Infect Dis J*. 2015;34(4):383-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25247583>.
28. Havens PL, Perumean-Chaney SE, Patki A, et al. Changes in bone mass after discontinuation of pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/emtricitabine in young men who have sex with men: extension Phase results of adolescent trials network protocols 110 and 113. *Clin Infect Dis*. 2019; 70(4):687-691 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31179503>.
29. Havens PL, Stephensen CB, Van Loan MD, et al. Vitamin D3 supplementation increases spine bone mineral density in adolescents and young adults with human immunodeficiency virus infection being treated with tenofovir disoproxil fumarate: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2018;66(2):220-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29020329>.
30. Havens PL, Long D, Schuster GU, et al. Tenofovir disoproxil fumarate appears to disrupt the relationship of vitamin D and parathyroid hormone. *Antivir Ther*. 2018;23(7):623-628. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30260797>.
31. Overton ET, Chan ES, Brown TT, et al. Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: a randomized trial. *Ann Intern Med*. 2015;162(12):815-824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26075752>.
32. Havens PL, Stephensen CB, Hazra R, et al. Vitamin D3 decreases parathyroid hormone in HIV-infected youth being treated with tenofovir: a randomized, placebo-controlled trial. *Clin Infect Dis*. 2012;54(7):1013-1025. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22267714>.
33. Eckard AR, O'Riordan MA, Rosebush JC, et al. Effects of vitamin D supplementation on bone mineral density and bone markers in HIV-infected youth. *J Acquir Immune Defic Syndr*. 2017;76(5):539-546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28902705>.
34. Havens PL, Kiser JJ, Stephensen CB, et al. Association of higher plasma vitamin D binding protein and lower free calcitriol levels with tenofovir disoproxil fumarate use and plasma and intracellular tenofovir pharmacokinetics: cause of a functional vitamin D deficiency? *Antimicrob Agents Chemother*. 2013;57(11):5619-5628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24002093>.
35. Van Welzen BJ, Thielen MAJ, Mudrikova T, Arends JE, Hoepelman AIM. Switching tenofovir disoproxil fumarate to tenofovir alafenamide results in a significant decline in parathyroid hormone levels: uncovering the mechanism of

tenofovir disoproxil fumarate-related bone loss? *AIDS*. 2019;33(9):1531-1534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31021851>.

36. DiMeglio LA, Wang J, Siberry GK, et al. Bone mineral density in children and adolescents with perinatal HIV infection. *AIDS*. 2013;27(2):211-220. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23032412>.
37. Yin MT, Lund E, Shah J, et al. Lower peak bone mass and abnormal trabecular and cortical microarchitecture in young men infected with HIV early in life. *AIDS*. 2014;28(3):345-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24072196>.
38. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis*. 2010;51(5):496-505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20673002>.
39. Hall AM. Update on tenofovir toxicity in the kidney. *Pediatr Nephrol*. 2013;28(7):1011-1023. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22878694>.
40. Andiman WA, Chernoff MC, Mitchell C, et al. Incidence of persistent renal dysfunction in human immunodeficiency virus-infected children: associations with the use of antiretrovirals, and other nephrotoxic medications and risk factors. *Pediatr Infect Dis J*. 2009;28(7):619-625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19561425>.
41. Wood SM, Shah SS, Steenhoff AP, Meyers KE, Kaplan BS, Rutstein RM. Tenofovir-associated nephrotoxicity in two HIV-infected adolescent males. *AIDS Patient Care STDS*. 2009;23(1):1-4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19183077>.
42. Hussain S, Khayat A, Tolaymat A, Rathore MH. Nephrotoxicity in a child with perinatal HIV on tenofovir, didanosine and lopinavir/ritonavir. *Pediatr Nephrol*. 2006;21(7):1034-1036. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16773419>.
43. Lucey JM, Hsu P, Ziegler JB. Tenofovir-related Fanconi's syndrome and osteomalacia in a teenager with HIV. *BMJ Case Reports*. 2013;2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23843401>.
44. Papaleo A, Warszawski J, Salomon R, et al. Increased beta-2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J*. 2007;26(10):949-951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17901802>.
45. Soler-Palacin P, Melendo S, Noguera-Julian A, et al. Prospective study of renal function in HIV-infected pediatric patients receiving tenofovir-containing HAART regimens. *AIDS*. 2011;25(2):171-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21076275>.
46. Purswani M, Patel K, Kopp JB, et al. Tenofovir treatment duration predicts proteinuria in a multiethnic United States cohort of children and adolescents with perinatal HIV-1 infection. *Pediatr Infect Dis J*. 2013;32(5):495-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23249917>.
47. Poizot-Martin I, Solas C, Allemand J, et al. Renal impairment in patients receiving a tenofovir-cART regimen: impact of tenofovir trough concentration. *J Acquir Immune Defic Syndr*. 2013;62(4):375-380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23196828>.
48. Rodriguez-Novoa S, Labarga P, D'Avolio A, et al. Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations. *AIDS*. 2010;24(7):1064-1066. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20299966>.
49. Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs tenofovir disoproxil fumarate: A pooled analysis of 26 clinical trials. *AIDS*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30932951>.
50. Sise ME, Hirsch JS, Canetta PA, Herlitz L, Mohan S. Nonalbumin proteinuria predominates in biopsy-proven tenofovir nephrotoxicity. *AIDS*. 2015;29(8):941-946. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25784440>.
51. Samarawickrama A, Cai M, Smith ER, et al. Simultaneous measurement of urinary albumin and total protein may facilitate decision-making in HIV-infected patients with proteinuria. *HIV Med*. 2012;13(9):526-532. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22413854>.

# Zidovudine (ZDV, Retrovir) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Capsule:** 100 mg

**Syrup:** 10 mg/mL

**Concentrate for Injection or Intravenous Infusion:** 10 mg/mL (Retrovir)

### Generic Formulations:

- 100 mg capsule
- 10 mg/mL syrup
- 300 mg tablet

### Fixed-Dose Combination Tablets:

- [Combivir and generic] Lamivudine 150 mg/zidovudine 300 mg (scored)
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

## Dosing Recommendations

**Note:** Zidovudine (ZDV) is frequently used in neonates to prevent perinatal transmission of HIV. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and [Table 12](#) for information about using ZDV to prevent perinatal transmission.

### Recommended Neonatal Dose for Treatment of HIV by Gestational Age at Birth<sup>a</sup>

Gestational Age at Birth	Oral ZDV Dose								
≥35 weeks	<b>Birth to Age 4 Weeks:</b> <ul style="list-style-type: none"><li>• ZDV 4 mg/kg twice daily; <i>or</i></li><li>• Alternative simplified weight-band dosing</li></ul> <b>Simplified Weight-Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth:</b> <p><b>Note:</b> The doses in this table provide approximately ZDV 4 mg/kg twice daily from birth to age 4 weeks.</p> <table border="1"><thead><tr><th>Weight Band</th><th>Twice-Daily Volume of ZDV 10 mg/mL Syrup</th></tr></thead><tbody><tr><td>2 kg to &lt;3 kg</td><td>1 mL</td></tr><tr><td>3 kg to &lt;4 kg</td><td>1.5 mL</td></tr><tr><td>4 kg to &lt;5 kg</td><td>2 mL</td></tr></tbody></table> <b>Aged &gt;4 Weeks:</b> <ul style="list-style-type: none"><li>• ZDV 12 mg/kg twice daily</li></ul>	Weight Band	Twice-Daily Volume of ZDV 10 mg/mL Syrup	2 kg to <3 kg	1 mL	3 kg to <4 kg	1.5 mL	4 kg to <5 kg	2 mL
Weight Band	Twice-Daily Volume of ZDV 10 mg/mL Syrup								
2 kg to <3 kg	1 mL								
3 kg to <4 kg	1.5 mL								
4 kg to <5 kg	2 mL								

## Selected Adverse Events

- Bone marrow suppression leading to anemia and neutropenia; macrocytosis with or without anemia.
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of ZDV) and myositis

## Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develops in patients who are receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- Screen patients for hepatitis B virus (HBV) infection before using FDC products that contain lamivudine (3TC). Severe acute exacerbation of HBV infection can occur when 3TC is discontinued; therefore, hepatic

Gestational Age at Birth	Oral ZDV Dose
≥30 weeks to <35 weeks	<p><b>Birth to Age 2 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 2 mg/kg twice daily</li> </ul> <p><b>Aged 2 Weeks to 6 to 8 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 3 mg/kg twice daily</li> </ul> <p><b>Aged &gt;6 Weeks to 8 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 12 mg/kg twice daily</li> </ul>
<30 weeks	<p><b>Birth to Age 4 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 2 mg/kg twice daily</li> </ul> <p><b>Aged 4 Weeks to 8 to 10 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 3 mg/kg twice daily</li> </ul> <p><b>Aged &gt;8 Weeks to 10 Weeks:</b></p> <ul style="list-style-type: none"> <li>ZDV 12 mg/kg twice daily</li> </ul>

**Note:** For infants who are unable to tolerate oral agents, the intravenous dose should be 75% of the oral dose, but the dosing interval should remain the same.

### Infant (Aged ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery, Weighing ≥4 kg) and Child Dose

#### Weight-Based Dosing for Zidovudine

Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

#### Alternative Body Surface Area Dosing

Oral:

- ZDV 180 mg to 240 mg per m<sup>2</sup> of body surface area every 12 hours

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

- ZDV 300 mg twice daily

#### [Combivir and Generic] Lamivudine/Zidovudine

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

- One tablet twice daily

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

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

- One tablet twice daily

function should be monitored for several months after patients with HBV infection stop taking 3TC.

#### Metabolism/Elimination

- ZDV is eliminated primarily by hepatic metabolism. The major metabolite is ZDV glucuronide, which is renally excreted.
- ZDV is phosphorylated intracellularly to active ZDV-triphosphate.

#### Zidovudine Dosing in Patients with Renal Impairment:

- A dose adjustment is required for ZDV in patients with renal insufficiency.

#### Zidovudine Dosing in Patients with Hepatic Impairment:

- The dose of ZDV may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min, patients who are on dialysis, or patients who have impaired hepatic function.

<sup>a</sup> For premature infants who receive an HIV diagnosis, the time to change to the continuation dose varies with post-gestational age and clinical status of the infant.

**Drug Interactions** (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 (ZDV).
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues, such as ribavirin, antagonize *in vitro* antiviral activity of ZDV.
- *Doxorubicin:* Simultaneous use of doxorubicin and ZDV **should be avoided**. Doxorubicin may inhibit the phosphorylation of ZDV to its active form.

### **Major Toxicities**

- *More common:* Hematologic toxicity, including neutropenia and anemia, particularly in patients with advanced HIV disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants who are receiving both lamivudine (3TC) and ZDV than in infants who are receiving only ZDV.<sup>1</sup>
- *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.<sup>2,3</sup>

### **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*

ZDV is frequently included as a component of the nucleoside reverse transcriptase inhibitor (NRTI) backbone for antiretroviral therapy (ART), and it has been studied in children in combination with other NRTIs, including abacavir (ABC) and 3TC.<sup>4-20</sup> Pediatric experience with ZDV both for treating HIV and for preventing perinatal transmission is extensive. However, the mitochondrial toxicity of ZDV leads many experts to favor the use of ABC or tenofovir alafenamide in cases where the patient's age and the results of viral resistance testing do not restrict the use of these drugs.

#### *Efficacy in Clinical Trials*

The combination of ZDV and 3TC has been extensively studied in children and has been a part of antiretroviral (ARV) regimens in many trials. The safety and efficacy of ZDV plus 3TC were compared to the safety and efficacy of ABC plus 3TC and stavudine (d4T) plus 3TC in children aged <5 years in the CHAPAS-3 study. All regimens also included either nevirapine or efavirenz. All the NRTIs had low toxicity and produced good clinical, immunologic, and virologic responses.<sup>21</sup> Pediatric patients who received ZDV plus ABC or ZDV plus 3TC had lower rates of viral suppression and experienced more adverse events that required regimen modification than patients who received ABC plus 3TC.<sup>22,23</sup>

#### *Infants with Perinatal HIV Exposure*

The PACTG 076 clinical trial demonstrated that administering ZDV to pregnant women and their infants could reduce the risk of perinatal HIV transmission by nearly 70%.<sup>24</sup> See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) for further discussion on using ZDV to prevent perinatal transmission of HIV. A dose of approximately ZDV 4 mg/kg of body weight every 12 hours is recommended for prevention of perinatal HIV transmission in neonates and infants with gestational ages  $\geq 35$  weeks. Infants who have been exposed to HIV but who are uninfected should continue on the prophylactic

dose for 4 to 6 weeks, depending on their gestational age at time of delivery and the risk assessment for perinatal transmission.

Simplified, alternative weight-band dosing has also been developed, and the rationale for these doses is based on the intracellular metabolism of ZDV (see Pharmacokinetics below). The rate-limiting step in the phosphorylation of ZDV to active ZDV triphosphate is the limited amount of thymidylate kinase. Increasing the dose of ZDV will lead to increased ZDV plasma concentrations and increased intracellular concentrations of ZDV monophosphate, but not ZDV diphosphate or ZDV triphosphate.

In 31 infants who received ZDV to prevent perinatal transmission, levels of intracellular ZDV metabolites were measured after delivery. Plasma ZDV and intracellular ZDV monophosphate decreased by roughly 50% between post-delivery Day 1 and Day 28, whereas ZDV diphosphate and ZDV triphosphate remained low throughout the sampling period.<sup>25</sup> ZDV dose is poorly correlated with the active form of ZDV that is found intracellularly. Because of this, a simplified weight-band dosing approach can be used for the first 4 weeks of life in infants with gestational ages  $\geq 35$  weeks (see the dosing table above). This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during ZDV use in the first 4 weeks of life and will make it easier for caregivers to administer ZDV oral syrup to their infants. The changes in weight and the small differences in ZDV dose will have minor effects on the intracellular concentrations of ZDV triphosphate.

### *Infants with HIV Infection*

For full-term neonates who receive an HIV diagnosis during the first days to weeks of life, the ZDV dose should be increased to the continuation dose at age 4 weeks (see the dosing table above). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically during the first 4 to 6 weeks of life in full-term neonates. This increase in metabolizing enzyme activity leads to an increased clearance of plasma ZDV, and the dose of ZDV should be adjusted when ZDV is used to treat HIV after the first 4 weeks in full-term infants.

For premature infants who receive an HIV diagnosis, the time to increase the ZDV dose from the initial dose varies with post-gestational age and the clinical status of the neonate. On the basis of population pharmacokinetic (PK) modeling and simulations and data from studies that have evaluated ZDV PKs in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends the following:

- For infants with HIV born at  $\geq 30$  weeks to  $< 35$  weeks, switch to a dose of ZDV 12 mg/kg twice daily at a post-gestational age of 6 to 8 weeks.
- For infants born at  $< 30$  weeks, switch to ZDV 12 mg/kg twice daily at a post-gestational age of 8 to 10 weeks.<sup>26</sup>

Clinicians should perform a careful clinical assessment of the infant, evaluate hepatic and renal function, and review concomitant medications before increasing the ZDV dose to the dose recommended for full-term infants.

### *Pharmacokinetics*

ZDV undergoes intracellular metabolism to achieve its active form, ZDV triphosphate. Phosphorylation requires multiple steps: ZDV is phosphorylated by thymidine kinase to ZDV monophosphate; ZDV monophosphate is phosphorylated by thymidylate kinase to ZDV diphosphate; and ZDV diphosphate is phosphorylated by nucleoside diphosphate kinase to ZDV triphosphate. Overall, ZDV PKs in pediatric patients aged  $> 3$  months are similar to those seen in adults. Although the mean half-life of intracellular ZDV triphosphate (9.1 hours) is considerably longer than that of unmetabolized ZDV in plasma (1.5 hours), once-daily ZDV dosing is not recommended because of the low intracellular ZDV triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.<sup>27</sup> PK studies such as PACTG 331 demonstrate that dose adjustments are necessary for premature infants, because they have reduced clearance of ZDV compared

with the clearance observed in term newborns of similar postnatal ages.<sup>5</sup> ZDV has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio is 0.68), and ZDV has been used in children with HIV-related CNS disease.<sup>16</sup>

### Toxicity

Several studies suggest that the adverse hematologic effects of ZDV may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean plasma area under the curve values for ZDV.<sup>4,5,28</sup> A significant reduction in the incidence of hematologic toxicity was observed during a retrospective analysis of infants who received a short course of ZDV (2 weeks) to prevent perinatal HIV transmission.<sup>29</sup> In this study, 137 infants received ZDV for 2 weeks, and 184 infants received ZDV for >2 weeks; of these infants, 168 (91.3%) received 4 weeks of ZDV prophylaxis. The risk of anemia (defined as a Division of AIDS [DAIDS] severity grade of mild or higher) was significantly lower in the short-course group at both age 1 month ( $P < 0.001$ ) and age 3 months ( $P < 0.001$ ).<sup>29</sup> Some national guidelines, including those from Germany/Austria and Great Britain, recommend a minimum of 2 weeks of post-exposure prophylaxis in infants at low risk or very low risk of HIV transmission.<sup>29,30</sup> Current U.S. guidelines recommend 4 weeks of prophylaxis for infants at low risk of HIV transmission. For infants who develop significant anemia while receiving ZDV for prevention of perinatal HIV transmission, early discontinuation may be considered for infants who are determined to be at a low risk of transmission after expert consultation.

Incidence of hematological toxicity was investigated in the ARROW study, which randomized ART-naive Ugandan and Zimbabwean children to receive either ZDV-containing regimens or ABC-containing regimens. The incidence of severe anemia was similar regardless of ZDV use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. ZDV use was associated with severe neutropenia in a small number of children.<sup>31</sup>

ZDV is associated with greater mitochondrial toxicity than ABC and tenofovir disoproxil fumarate, but it is associated with less mitochondrial toxicity than d4T.<sup>32,33</sup>

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 ZDV may increase the risk.<sup>2</sup> Analysis of data from a U.S.-based, multicenter, prospective cohort study (PACTG 219/219C) found that ongoing ZDV exposure was independently associated with a higher rate of cardiomyopathy.<sup>2</sup> As part of the Pediatric HIV/AIDS Cohort Study (PHACS)/Adolescent Master Protocol (AMP) study, echocardiogram measurements were collected between 2008 and 2010 in 325 youth aged 7 to 16 years with perinatally acquired HIV infection. An association between ZDV use and increased end-systolic wall stress was observed in this study. The investigators speculate that alterations in cardiac structure in these children could progress to symptomatic cardiomyopathy later in life.<sup>3</sup>

## References

1. Nielsen-Saines K, Watts DH, Veloso VG, et al. Three postpartum antiretroviral regimens to prevent intrapartum HIV infection. *N Engl J Med*. 2012;366(25):2368-2379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716975>.
2. Patel K, Van Dyke RB, Mittleman MA, et al. The impact of HAART on cardiomyopathy among children and adolescents perinatally infected with HIV-1. *AIDS*. 2012;26(16):2027-2037. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22781228>.
3. Williams PL, Correia K, Karalius B, et al. Cardiac status of perinatally HIV-infected children: assessing combination antiretroviral regimens in observational studies. *AIDS*. 2018;32(16):2337-2346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30102660>.
4. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. *Ann Intern Med*. 1989;110(4):279-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2643914>.

5. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr*. 2003;142(1):47-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12520254>.
6. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24(9):793-800. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16148846>.
7. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med*. 1997;336(24):1704-1712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9182213>.
8. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis*. 2001;183(7):1116-1120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11237839>.
9. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. *Clinical Pharmacokinet*. 2002;41(14):1115-1133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12405863>.
10. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. 1997;336(19):1343-1349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9134874>.
11. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med*. 1991;324(15):1018-1025. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1672443>.
12. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The pediatric AIDS clinical trials group protocol 300 study team. *J Pediatr*. 1998;133(4):500-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9787687>.
13. Mueller BU, Nelson RP, Jr., Sleasman J, et al. A Phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*. 1998;101(3 Pt 1):335-343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9480994>.
14. Mueller BU, Sleasman J, Nelson RP, Jr., et al. A Phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*. 1998;102(1 Pt 1):101-109. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9651421>.
15. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis*. 2002;34(1):41-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11874163>.
16. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med*. 1988;319(14):889-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3166511>.
17. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. *Pediatrics*. 2001;107(1):E4. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11134468>.
18. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):1008-1016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11880968>.
19. Bergshoeff AS, Fraaij PL, Verweij C, et al. Plasma levels of zidovudine twice daily compared with three times daily in six HIV-1-infected children. *J Antimicrob Chemother*. 2004;54(6):1152-1154. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15537694>.
20. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*.

- 2000;283(4):492-498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10659875>.
21. Mulenga V, Musiime V, Kekitiinwa A, et al. Abacavir, zidovudine, or stavudine as paediatric tablets for African HIV-infected children (CHAPAS-3): an open-label, parallel-group, randomised controlled trial. *Lancet Infect Dis*. 2016;16(2):169-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26481928>.
  22. Green H, Gibb DM, Walker AS, et al. Lamivudine/abacavir maintains virological superiority over zidovudine/lamivudine and zidovudine/abacavir beyond 5 years in children. *AIDS*. 2007;21(8):947-955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17457088>.
  23. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002;359(9308):733-740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11888583>.
  24. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331(18):1173-1180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7935654>.
  25. Kinai E, Kato S, Hosokawa S, et al. High plasma concentrations of zidovudine (AZT) do not parallel intracellular concentrations of AZT-triphosphates in infants during prevention of mother-to-child HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2016;72(3):246-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26859826>.
  26. Capparelli EV, Englund JA, Connor JD, et al. Population pharmacokinetics and pharmacodynamics of zidovudine in HIV-infected infants and children. *J Clin Pharmacol*. 2003;43(2):133-140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12616665>.
  27. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother*. 2007;51(10):3516-3522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17664328>.
  28. Fillekes Q, Kendall L, Kitaka S, et al. Pharmacokinetics of zidovudine dosed twice daily according to world health organization weight bands in Ugandan HIV-infected children. *Pediatr Infect Dis J*. 2014;33(5):495-498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24736440>.
  29. Nguyen TTT, Kobbe R, Schulze-Sturm U, et al. Reducing hematologic toxicity with short course postexposure prophylaxis with zidovudine for HIV-1 exposed infants with low transmission risk. *Pediatr Infect Dis J*. 2019;38(7):727-730. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31033907>.
  30. British HIV Association. BHIVA guidelines on the management of HIV in pregnancy and postpartum 2018 (2019 interim update). 2019. Available at: <https://www.bhiva.org/pregnancy-guidelines>.
  31. Musiime V, Cook A, Nahirya Ntege P, et al. The effect of long-term zidovudine on hematological parameters in the ARROW randomized trial. Presented at: The Conference on Retroviruses and Opportunistic Infections. 2015. Seattle, Washington.
  32. Moyle GJ, Sabin CA, Cartledge J, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. *AIDS*. 2006;20(16):2043-2050. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17053350>.
  33. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *JAMA*. 2002;288(2):207-215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12095385>.

## **Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)**

Doravirine (DOR, Pifeltro)

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant)

## Doravirine (DOR, Pifeltro) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

**Tablet:** 100 mg

#### Fixed-Dose Combination Tablet:

- [Delstrigo] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Child and Adolescent Dose:

- Doravirine (DOR) is not approved for use in children or adolescents aged <18 years.

#### Adult (Aged ≥18 Years) Dose:

- DOR 100 mg once daily in antiretroviral (ARV)-naive patients and ARV-experienced patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen with no history of treatment failure and no known mutations associated with resistance to DOR.

#### [Delstrigo] Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF)

*Adult (Aged ≥18 Years) Dose:*

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

### Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

### Special Instructions

- DOR can be taken with or without food.
- **Do not use** DOR with other non-nucleoside reverse transcriptase inhibitors.
- When DOR is coadministered with rifabutin, the dose should be increased from DOR 100 mg once daily to DOR 100 mg twice daily. When doravirine/lamivudine/TDF (DOR/3TC/TDF; Delstrigo) is coadministered with rifabutin, an additional 100-mg dose of freestanding DOR needs to be administered approximately 12 hours later.
- Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains 3TC and TDF. Severe acute exacerbation of HBV can occur when 3TC or TDF are discontinued; therefore, hepatic function and hepatitis B viral load should be monitored for several months after halting therapy with 3TC or TDF.

### Metabolism/Elimination

- DOR is metabolized by the enzyme cytochrome P450 3A.
- DOR has multiple interactions with several drugs (see text below).

### Doravirine Dosing in Patients with Hepatic Impairment:

- Dose adjustment is not required in patients with mild or moderate hepatic impairment. DOR has not been studied in patients with severe hepatic impairment.

### Doravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required when using DOR in patients with mild, moderate, or severe renal impairment. DOR use has not been studied in patients with end-stage renal disease or in patients on dialysis.
- DOR administered with 3TC and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

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

- Doravirine (DOR) is a cytochrome P450 (CYP) 3A substrate that is associated with several important drug interactions with drugs that are strong CYP3A enzyme inducers. Coadministration with these drugs may cause significant decreases in DOR plasma concentrations and potential decreases in efficacy and may lead to the development of resistance. Before DOR is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with DOR.<sup>1,2</sup>
- DOR **should not be coadministered** with the CYP3A inducing non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz (EFV), etravirine, and nevirapine.<sup>3,4</sup> **In a Phase 1 trial (see below), DOR plasma exposure transiently decreased by 62% when DOR was started immediately after stopping EFV. However, a post-hoc analysis of the Phase 3 DRIVE-SHIFT study (see below) showed that, at Week 4, DOR plasma levels in patients who had switched from an EFV-based regimen to a DOR-based regimen were similar to DOR plasma levels in patients who switched from a protease inhibitor (PI)-based regimen to a DOR-based regimen (all the regimens in the study used a backbone of lamivudine [3TC] plus tenofovir disoproxil fumarate [TDF]).<sup>3</sup>**
- DOR **should not be coadministered** with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; or St. John's wort.<sup>3,4</sup>
- Drug interactions between DOR and rifabutin induce the metabolism of DOR and require an additional dose of DOR 100 mg to be administered 12 hours later.<sup>2,4</sup>

### Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams.
- *Less common (more severe):* Neuropsychiatric adverse events (AEs), including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

## Resistance

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

DOR is expected to have activity against HIV with isolated NNRTI resistance that is associated with substitutions at positions 103, 181, or 190. However, some single mutations and combinations of viral mutations have been shown to significantly decrease the susceptibility to DOR. Specifically, clinical HIV isolates containing the Y188L substitution alone or in combinations with K103N or V106I; combinations of V106A with G190A and F227L; or combinations of E138K with Y181C and M230L have shown  $\geq 100$ -fold reduction in susceptibility to DOR.<sup>3,4</sup> In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of DOR.

## Pediatric Use

### Approval

DOR is not approved by the Food and Drug Administration for use in children or adolescents aged <18 years. An ongoing Phase 1/2 study ([IMPAACT 2014](#)) is evaluating the pharmacokinetics (PKs), safety, and tolerability of DOR and DOR/3TC/TDF in children and adolescents with HIV.

### Efficacy in Clinical Trials

The efficacy of DOR was evaluated using data from four randomized adult clinical trials. The first study was a Phase 2b dose-selection, double-blind trial that enrolled treatment-naïve adults with HIV.<sup>6</sup> The efficacy trials included two randomized, multicenter, double-blind, active-controlled Phase 3 trials ([DRIVE-FORWARD](#) and [DRIVE-AHEAD](#)) in treatment-naïve adults<sup>7,8</sup> and one open-label, active-controlled, randomized, noninferiority trial that enrolled virologically suppressed adults on antiretroviral therapy ([DRIVE-SHIFT](#)).<sup>9</sup>

The dose-selection trial enrolled treatment-naïve adults stratified by HIV RNA level at screening ( $\leq 100,000$  copies/mL or  $> 100,000$  copies/mL) and randomized participants to receive one of four different doses (25 mg, 50 mg, 100 mg, or 200 mg) of once-daily DOR or EFV 600 mg with open-label emtricitabine (FTC) 200 mg/TDF 300 mg. After dose selection at Week 24, all participants were switched to DOR 100 mg and, with additional enrollment, 216 participants were randomized to receive once-daily DOR 100 mg (n = 108) or EFV 600 mg (n = 108) for 96 weeks with FTC/TDF. At Week 24, 72.9% of participants on DOR 100 mg and 73.1% of participants on EFV 600 mg had HIV RNA  $< 40$  copies/mL.<sup>6</sup>

In DRIVE-FORWARD, adult subjects received either DOR 100 mg (n = 383) or darunavir 800 mg/ritonavir 100 mg (DRV/r; n = 383) once daily, each in combination with FTC/TDF or abacavir/3TC.<sup>7</sup> In DRIVE-AHEAD, adult subjects received either coformulated DOR/3TC/TDF (n = 364) or EFV/FTC/TDF (n = 364) once daily.<sup>8</sup> An integrated efficacy analysis from both trials (DRIVE-FORWARD and DRIVE-AHEAD) at Week 48 demonstrated that 84.1% of patients who were treated with the DOR-based regimen achieved HIV RNA  $< 50$  copies/mL compared to 79.9% of patients who were treated with the DRV/r-based regimen and 80.8% of patients who were treated with EFV/FTC/TDF. There were similar results across different baseline viral loads, genders, races, and HIV-1 subtypes.<sup>8</sup>

In the DRIVE-SHIFT study, adult subjects with HIV who were virologically suppressed for  $\geq 6$  months on two nucleoside reverse transcriptase inhibitors plus a boosted PI, boosted elvitegravir, or an NNRTI were randomized to switch to a once-daily, single-tablet regimen of DOR 100 mg/3TC 300 mg/TDF 300 mg or to continue their current therapy (baseline regimen). At Weeks 24 and 48, 93.7% and 90.8% of participants on the DOR/3TC/TDF regimen, respectively, had HIV RNA  $< 50$  copies/mL, demonstrating the noninferiority of this regimen compared to the baseline regimen at Week 24.<sup>9</sup>

## Pharmacokinetics

The PKs of DOR have been evaluated in treatment-naïve adults aged  $\geq 18$  years. A Phase 2 trial evaluated DOR over a dose range of 0.25 times to two times the recommended dose in treatment-naïve participants with

HIV who also received FTC/TDF. No exposure-response relationship for efficacy was reported for DOR.<sup>8</sup>

### Toxicity

In trials that compared DOR-based and EFV-based regimens, central nervous system (CNS) AEs (dizziness, sleep disorder and disturbances, and altered sensorium) occurred less frequently among the patients who received DOR compared to those who received EFV. In the dose-finding trial, CNS AEs were reported in 26.9% of patients on DOR-based regimens compared to 47.2% of patients on EFV-based regimens at Week 24.<sup>6</sup> In the integrated safety analysis from the DRIVE-FORWARD and DRIVE-AHEAD trials, 25.5% of patients on DOR-based regimens experienced CNS AEs at Week 48 compared to 55.9% of patients on EFV-based regimens.<sup>8,10</sup> Neither DRIVE-FORWARD nor DRIVE-AHEAD included an integrase strand transfer inhibitor-based regimen as an active control. Fewer participants who received DOR-based regimens experienced diarrhea compared to those treated with DRV/r-based regimens (12.4% vs. 22.5%, respectively). In the DRIVE-SHIFT study, among adults who were receiving a ritonavir-boosted PI at study entry, mean reductions in fasting low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol at Week 24 were significantly greater in people who received DOR/3TC/TDF compared to the baseline PI-based regimen with 3TC/TDF ( $P < 0.0001$ ).<sup>9</sup>

### References

1. Boyle A, Moss CE, Marzolini C, Khoo S. Clinical pharmacodynamics, pharmacokinetics, and drug Interaction profile of doravirine. *Clinical Pharmacokinet*. 2019;58(12):1553-1565. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31388941>.
2. Khalilieh SG, Yee KL, Sanchez RI, et al. Doravirine and the potential for CYP3A-mediated drug-drug interactions. *Antimicrob Agents Chemother*. 2019;63(5). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30783000>.
3. Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/210807s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210807s0031bl.pdf).
4. Doravirine [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/210806s0031bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210806s0031bl.pdf).
5. Greaves W, Wan H, Yee KL, Kandala B, Vaddady P, Hwang C. Doravirine exposure and HIV-1 suppression after switching from an efavirenz-based regimen to doravirine/lamivudine/tenofovir disoproxil fumarate. *Antimicrob Agents Chemother*. 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31548188>.
6. Gatell JM, Morales-Ramirez JO, Hagins DP, et al. Doravirine dose selection and 96-week safety and efficacy versus efavirenz in antiretroviral therapy-naive adults with HIV-1 infection in a Phase IIb trial. *Antivir Ther*. 2019; 24(6):425-435. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31355775>.
7. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(5):e211-e220. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29592840>.
8. Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD Trial. *Clin Infect Dis*. 2019;68(4):535-544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30184165>.
9. Johnson M, Kumar P, Molina JM, et al. Switching to doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) maintains HIV-1 virologic suppression through 48 weeks: results of the DRIVE-SHIFT Trial. *J Acquir Immune Defic Syndr*. 2019;81(4):463-472. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30985556>.
10. Thompson M, Orkin C, Molina JM, et al. Once-daily doravirine for initial treatment of adults living with HIV-1: an integrated safety analysis. *Clin Infect Dis*. 2019;pii: ciz423 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31121013>.

# Efavirenz (EFV, Sustiva) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Capsules:** 50 mg, 200 mg

**Tablet:** 600 mg

### Generic Formulations:

- 50 mg and 200 mg capsules
- 600 mg tablet

### Fixed-Dose Combination Tablets:

- [Atripla and generic] Efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi] Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg
- [Symfi Lo] Efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

## Dosing Recommendations

### Neonatal Dose:

- Efavirenz (EFV) is not approved for use in neonates.

### Pediatric Dose:

- EFV capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.

*Infants and Children Aged 3 Months to <3 Years and Weighing  $\geq$  3.5 kg:*

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of EFV in children aged 3 months to <3 years due to highly variable pharmacokinetics in this age group.
- If the use of EFV is unavoidable due to a clinical situation, the Panel suggests using investigational doses of EFV in this age group (see Table A in the Pharmacokinetics and Dosing: Infants and Children Aged <3 Years section below). Evaluation of cytochrome P450 (CYP) 2B6 genotype is required prior to use of EFV in this age group. Therapeutic drug monitoring (TDM) should be used and EFV plasma concentration should be measured 2 weeks after initiation. If a child initiated

## 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, **late-onset ataxia, and encephalopathy**
- Use of EFV may produce false-positive results with some cannabinoid and benzodiazepine tests.
- Gynecomastia
- Hepatotoxicity
- Corrected QT prolongation

## Special Instructions

- EFV capsules and tablets can be swallowed whole, or EFV capsules can be administered by sprinkling the contents of an opened capsule on food as described below.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of CNS side effects.
- Administer EFV, Atripla, Symfi, or Symfi Lo on an empty stomach. Avoid administration with

EFV at an investigational dose while aged <3 years, some experts would also measure EFV plasma concentration at age 3 years after the child transitions to the recommended dose for children aged ≥3 years (see the [Therapeutic Drug Monitoring](#) section below). When making a dose adjustment based on EFV 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	EFV Dose <sup>a,b</sup>
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

<sup>a</sup> 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).

<sup>b</sup> Some experts recommend a dose of EFV 367 mg per m<sup>2</sup> of body surface area (maximum dose 600 mg) due to concerns about underdosing at the upper end of each weight band (see the Pediatric Use section below for details). Weight bands approximate a dose of EFV 367 mg per m<sup>2</sup> of body surface area, with a maximum dose of 600 mg.

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

- EFV 600 mg once daily

#### **Atripla** Efavirenz 600 mg/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

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

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

#### **Symfi** Efavirenz 600 mg/Lamivudine/TDF

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

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

#### **Symfi Lo** Efavirenz 400 mg/Lamivudine/TDF

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

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

a high-fat meal, because this has the potential to increase absorption.

- The Food and Drug Administration cautions that EFV should not be used during the first trimester of pregnancy because of potential teratogenicity. However, after a review of updated evidence regarding teratogenicity risks, the [Perinatal Guidelines](#) do not restrict use of EFV in female adolescents and adults who are pregnant or who may become pregnant.

#### Instructions for Using the Efavirenz Capsule as a Sprinkle Preparation with Food or Formula:

- Hold capsule horizontally over a small container and carefully twist open to avoid spillage.
- Gently mix capsule contents with 1 to 2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

#### Metabolism/Elimination

- CYP2B6 is the primary enzyme for EFV metabolism.
- CYP3A and CYP2B6 inducer *in vivo*
- EFV **is not recommended** for patients with moderate or severe hepatic impairment.
- Interpatient variability in EFV exposure can be explained in part by polymorphisms in CYP450, particularly CYP2B6 polymorphisms. Slower metabolizers are at higher risk of toxicity (see the Therapeutic Drug Monitoring section below for information about the management of mild or moderate toxicity).

#### Atripla, Symfi, and Symfi Lo Dosing in Adults with Renal Impairment:

- Because these are FDC products, and because 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 ratings [SMRs] 1–3), and major interindividual variability in EFV plasma concentrations has been found in pediatric patients in a multiethnic setting. The 400 mg dose of EFV may be too low in children or adolescents with SMRs 1 to 3 who weigh  $\geq 40$  kg. The use of TDM is suggested by some Panel members when Symfi Lo is used in pediatric patients who weigh  $\geq 40$  kg (see the [Therapeutic Drug Monitoring](#) section below).

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

- **Metabolism:** Coadministration of efavirenz (EFV) with drugs that are primarily metabolized by cytochrome P450 (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the coadministered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of EFV, resulting in lower plasma concentrations. There is potential for multiple drug interactions with EFV. Importantly, dose adjustment or the addition of ritonavir may be necessary when EFV is used in combination with atazanavir (ATV), lopinavir/ritonavir (LPV/r), or maraviroc (MVC).
- Before EFV is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with EFV.
- Corrected QT (QTc) prolongation has been observed with the use of EFV.<sup>1,2</sup> Consider using an alternative to EFV in patients who are receiving a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

### **Major Toxicities**

- **More common:** Skin rash, increased transaminase levels. Central nervous system (CNS) abnormalities such as dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria, and seizures have been reported, primarily in adults (see [Table 15a](#) for information on managing these toxicities).
- **Rare:** QTc prolongation has been observed with the use of EFV.<sup>1,2</sup> A case report associated EFV use with marked QT prolongation and Torsades de Pointes.<sup>3</sup> An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.
- **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*

EFV has been approved by the Food and Drug Administration (FDA) for use as part of antiretroviral (ARV) therapy in children aged  $\geq 3$  months and weighing  $\geq 3.5$  kg. The FDA has also approved the use of Symfi Lo,

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the fixed-dose combination of EFV 400 mg/lamivudine (3TC) 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing  $\geq 35$  kg.

### *Efficacy in Clinical Trials*

EFV-based regimens have proven virologically superior or noninferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, ATV, elvitegravir, raltegravir, and MVC.<sup>4-10</sup> EFV was shown to be inferior to dolutegravir (DTG) in the SINGLE trial in adults, which compared the virologic response of DTG plus abacavir/3TC to the virologic response of EFV/TDF/emtricitabine (FTC) at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the EFV group.<sup>11</sup>

In clinical trials in adults and children with HIV, EFV used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response. FDA approval of Symfi (EFV 600 mg/3TC/TDF) was based on the results from a clinical trial that compared the use of TDF to the use of stavudine when each drug was administered with 3TC and EFV.<sup>12</sup> This trial showed that these regimens were similarly effective. The 96-week results of the Encore1 trial, a randomized trial in adults, showed that EFV 400 mg used in combination with TDF and FTC was noninferior to EFV 600 mg used in combination with TDF and FTC.<sup>13</sup> EFV 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.<sup>14-20</sup>

FDA approval of Symfi Lo (EFV 400 mg/3TC/TDF) was based on a comparison between EFV 400 mg and EFV 600 mg, both taken with FTC 200 mg plus TDF 300 mg in 630 ARV-naïve 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.<sup>13</sup> Since EFV 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) suggest using therapeutic drug monitoring (TDM) **when using Symfi Lo in pediatric patients weighing  $\geq 40$  kg.**

### *Pharmacokinetics: Pharmacogenomics*

Genetic polymorphisms in the genes that code for enzymes involved in the metabolism of EFV may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for EFV metabolism, and pediatric patients with the CYP2B6-516-T/T genotype have reduced metabolism, resulting in higher EFV levels in these patients than in those with the G/G or G/T genotypes.<sup>21-25</sup> 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.<sup>26</sup> A retrospective study of pediatric patients in a multi-ethnic, high-income setting confirmed that EFV plasma concentrations can vary between patients. The interindividual variability could be explained in large part by polymorphisms in drug metabolizing genes, as well as by age at treatment initiation and time since treatment initiation.<sup>27</sup> IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/kg of EFV using opened capsules resulted in therapeutic EFV concentrations in 58% of children aged  $< 3$  years with the G/G or G/T genotypes, but excessive exposure occurred in those with the T/T genotype.<sup>28</sup> Optimal dosing may require pretreatment CYP2B6 genotyping in children aged  $< 3$  years (see discussion below).<sup>25,28</sup>

Other variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence EFV concentrations in adults and children.<sup>25,29-33</sup> The CYP2B6 T983C mutation has also been associated with reduced EFV clearance in African children.<sup>25</sup>

### *Pharmacokinetics and Dosing: Infants and Children Aged $< 3$ Years*

The Panel **does not recommend** the use of EFV in children aged 3 months to  $< 3$  years. Limited pharmacokinetic (PK) data in children aged  $< 3$  years or weighing  $< 13$  kg have shown that it is difficult

to achieve target trough concentrations in this age group.<sup>23,34</sup> These data show age-related differences in absorption and the impact of formulation on EFV PKs.<sup>24</sup> Also, hepatic enzyme activity is known to change with age. Using a pharmacometric model, the increase in oral clearance of EFV as a function of age is predicted to reach 90% of mature value by age 9 months.<sup>24</sup> This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.<sup>24</sup> 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.<sup>21</sup> In children with the CYP2B6-516-G/G genotype, the oral clearance rate of EFV has been shown to be higher in children aged <5 years than in older children.<sup>21</sup> Efficacy data for opened capsules with contents used as a sprinkle preparation suggest acceptable palatability and bioavailability for infants and children aged <3 years; however, the difficulty associated with sprinkling the contents of opened capsules contributes to the variability of PK measures in this age group.

IMPAACT P1070 studied children aged <3 years with HIV and tuberculosis (TB) coinfection, using doses of EFV that were determined by weight band based on CYP2B6-516-G/G and -G/T genotypes: children with G/G and G/T genotypes were considered extensive metabolizers (EMs) and children with T/T genotypes were considered slow metabolizers (SMs) (see Table A below). When doses were used without regard to genotype, a dose of approximately 40 mg/kg per day resulted in therapeutic EFV concentrations in an increased proportion of study participants with G/G or G/T genotypes but excessive exposure in a high proportion of participants with T/T genotypes. This dose is higher than the FDA-approved dose of EFV.<sup>28</sup> Therefore, doses were modified so that infants and young children with the T/T genotype received a reduced dose. The doses listed for P1070 in Table A are investigational.

A recent study evaluated the PKs of EFV in children aged <3 years who had TB/HIV coinfection and who were receiving anti-TB treatment with rifampicin, isoniazid, pyrazinamide, and ethambutol. The findings from this study reinforced the use of CYP2B6-516 genotype-directed EFV dosing and showed that, in general, the EFV weight-band dose did not need to be modified further for children aged <24 months. Dosing for children aged 24 to 36 months requires further investigation.<sup>35</sup>

*Investigational Dosing for Children Aged 3 Months to <3 Years By CYP2B6 Genotype*

**Table A. Comparison of Efavirenz Doses Used in P1070 and the FDA-Recommended Doses**

Weight	Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (EMs) <sup>a</sup>	Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (SMs) <sup>a</sup>	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

<sup>a</sup> Investigational doses are based on IMPAACT study P1070.<sup>28,35</sup> Evaluation of CYP2B6 genotype is required before initiating EFV. Therapeutic drug level monitoring is recommended, with a trough concentration measured 2 weeks after initiating EFV and again at age 3 years for a possible dose adjustment.

**Key:** CYP = cytochrome P450; EFV = efavirenz; EM = extensive metabolizer; FDA = Food and Drug Administration; SM = slow metabolizer

The FDA-approved doses of EFV for use in infants and children aged 3 months to <3 years were derived from a population PK model that was based on data from older subjects in PACTG 1021 and PACTG 382, and also from data collected during AI266-922, a study that assessed the PKs, safety, and efficacy of using capsule sprinkles in children aged 3 months to 6 years (see Table A). The FDA-approved doses are lower

than the CYP2B6 EM doses and higher than the CYP2B6 SM doses from the P1070 study. PK modeling, based on P1070 PK data, was used to generate estimates of the percentage of participants who were likely to reach therapeutic EFV target concentrations on FDA-indicated doses, according to the participants' genotypes.<sup>28</sup> The study reported that an estimated one-third of EM children who received the FDA-approved dose would experience subtherapeutic EFV exposures, and more than half of SM children who received the FDA-approved dose would have area under the curve (AUC) values that were above the target range.

The Panel **does not recommend** use of EFV in children aged 3 months to <3 years. If the clinical situation demands the use of EFV, the Panel recommends determining CYP2B6 genotype prior to use (see a [list of laboratories that perform this test](#)). Patients should be classified as extensive CYP2B6-516-G/G and -G/T genotype metabolizers or slow CYP2B6-516-T/T genotype metabolizers to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Table A). Whether the doses used are investigational or approved by the FDA, EFV plasma concentrations should be measured 2 weeks after initiating EFV (see the Therapeutic Drug Monitoring section below). The mid-dose EFV plasma concentration target of 1.0 mg/L to 4.0 mg/L derived from adult clinical monitoring data is typically also applied to trough concentrations. A study of 128 African children (aged 1.7–13.5 years) suggests that the C<sub>24h</sub> threshold for increased risk of unsuppressed viral load is C<sub>24h</sub> 0.65 mg/L.<sup>36</sup> 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 EFV concentrations at age 3 years before transitioning the child to the recommended dose for children aged ≥3 years.

#### *Pharmacokinetics: Children Aged ≥3 Years and Adolescents*

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, EFV concentrations can be suboptimal.<sup>21,37-41</sup> Therefore, some experts recommend using TDM in patients who are receiving EFV and possibly using higher doses in young children, especially in certain clinical situations, such as virologic rebound or lack of response in an adherent patient. In one study in which the EFV dose was adjusted in response to measurement of the AUC, the median administered dose was EFV 13 mg/kg (367 mg per m<sup>2</sup> of body surface area) and the range was from 3 mg/kg to 23 mg/kg (69–559 mg per m<sup>2</sup> of body surface area).<sup>42</sup>

#### *Toxicity: Children versus Adults*

The toxicity profile for EFV differs for adults and children. One adverse effect (AE) commonly seen in children is rash, which was reported in up to 40% of children and 27% of adults.<sup>43</sup> 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.<sup>44</sup> These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes persist for months. Administering EFV at bedtime appears to decrease the occurrence and severity of these neuropsychiatric AEs. For patients who can swallow capsules or tablets, ensuring that EFV is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. In several studies, the incidence of neuropsychiatric AEs was correlated with EFV plasma concentrations, and the symptoms occurred more frequently in patients with higher concentrations.<sup>45-48</sup> The ENCORE1 study in adults demonstrated that a dose of EFV 400 mg is associated with fewer AEs and a noninferior virologic response when compared with the recommended 600-mg dose of EFV.<sup>13,49</sup> **A Tanzanian study of children aged 6 to 12 years showed that those who were receiving EFV, especially doses of EFV that were higher than or equal to those recommended by the World Health Organization, had more anxiety and more difficulty concentrating at school than children who were receiving alternative ARV medications.**<sup>50</sup> Adverse CNS events occurred in 14% of children who received EFV in clinical studies<sup>51</sup> and in 30% of children with plasma EFV concentrations >4 mg/L.<sup>22</sup> **Late-onset neurotoxicity, including ataxia and encephalopathy, may occur months to years after initiating EFV. Some events of late-onset neurotoxicity have occurred in patients with certain CYP2B6 genetic polymorphisms who received standard doses of EFV. These polymorphisms have been**

associated with slow metabolism of EFV and increased EFV levels (see the package insert for EFV).

An association between EFV and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the START Trial, a prospective analysis of adults.<sup>52,53</sup> This association, however, was not found in analyses of two large observational cohorts,<sup>54,55</sup> and no cases of suicide were reported in a systematic review of randomized trials.<sup>44</sup> In patients with pre-existing psychiatric conditions, EFV should be used cautiously.

#### *Toxicity: QTc Prolongation*

The effect of EFV on the QTc interval was evaluated in a study of 58 healthy adult participants; a variety of CYP2B6 polymorphisms was represented within this group. A positive relationship between EFV concentration and QTc prolongation was observed.<sup>1</sup> Consider using an alternative to EFV in patients who are receiving a drug that has a known risk of Torsades de Pointes (e.g., quinidine, clarithromycin) or in patients who are at higher risk of Torsades de Pointes.<sup>2</sup>

#### *Therapeutic Drug Monitoring*

It is reasonable for a clinician to use TDM to determine whether a patient is experiencing toxicity because the concentration of EFV is higher than the normal therapeutic range.<sup>56,57</sup> Dose reduction or drug discontinuation would be considered appropriate management of drug toxicity. Dose reduction is best performed in consultation with an expert in pediatric HIV. Also, TDM should be considered when administering EFV to children aged 3 months to <3 years due to increased oral clearance and variable PK properties in this young age group. TDM should also be considered when using a lower dose of EFV, such as the dose found in Symfi Lo, in children weighing  $\geq 40$  kg. Two weeks after initiating EFV in patients aged <3 years, clinicians should measure the plasma concentration of EFV. In cases where a dose adjustment may be necessary, clinicians should consult an expert in pediatric HIV infection prior to adjusting the dose. If a child initiated EFV at an investigational dose 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  $\geq 3$  years.

The currently accepted minimum effective concentration of EFV is a mid-dose concentration ( $C_{12h}$ )  $>1$  mg/L in adults, and concentrations of  $>4.0$  mg/L are associated with CNS side effects.<sup>46</sup> However, the validity using a single target has been called into question.<sup>58</sup> In addition, a lower limit of  $C_{12h} >0.7$  mg/L was most predictive of virologic outcome in a study of 180 adults.<sup>59</sup> 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.<sup>36</sup>

## References

1. Abdelhady AM, Shugg T, Thong N, et al. Efavirenz inhibits the human ether-a-go-go related current (hERG) and induces QT interval prolongation in CYP2B6\*6\*6 allele carriers. *J Cardiovasc Electrophysiol*. 2016;27(10):1206-1213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27333947>.
2. Efavirenz [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020972s057,021360s0451bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020972s057,021360s0451bl.pdf).
3. Castillo R, Pedalino RP, El-Sherif N, Turitto G. Efavirenz-associated QT prolongation and torsade de pointes arrhythmia. *Ann Pharmacother*. 2002;36(6):1006-1008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12022902>.
4. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr*. 2004;36(5):1011-1019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15247553>.
5. Torti C, Maggiolo F, Patroni A, et al. Exploratory analysis for the evaluation of lopinavir/ritonavir-versus efavirenz-based HAART regimens in antiretroviral-naive HIV-positive patients: results from the Italian MASTER cohort. *J Antimicrob Chemother*. 2005;56(1):190-195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15917286>.

6. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18480202>.
7. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19647866>.
8. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. *J Infect Dis*. 2010;201(6):803-813. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20151839>.
9. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr*. 2012;60(1):33-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22343174>.
10. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials*. 2002;3(3):186-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12032877>.
11. Walmsley S, Baumgarten A, Berenguer J, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naive patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr*. 2015;70(5):515-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26262777>.
12. Margot NA, Lu B, Cheng A, Miller MD, Study 903 Team. Resistance development over 144 weeks in treatment-naive patients receiving tenofovir disoproxil fumarate or stavudine with lamivudine and efavirenz in Study 903. *HIV Med*. 2006;7(7):442-450. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16925730>.
13. ENCORE1 Study Group, Carey D, Puls R, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis*. 2015;15(7):793-802. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25877963>.
14. Fraaij PL, Bergshoeff AS, van Rossum AM, Hartwig NG, Burger DM, de Groot R. Changes in indinavir exposure over time: a case study in six HIV-1-infected children. *J Antimicrob Chemother*. 2003;52(4):727-730. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12917234>.
15. Funk MB, Notheis G, Schuster T, et al. Effect of first line therapy including efavirenz and two nucleoside reverse transcriptase inhibitors in HIV-infected children. *Eur J Med Res*. 2005;10(12):503-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16356864>.
16. McKinney RE, Jr., Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. *Pediatrics*. 2007;120(2):e416-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17646352>.
17. Spector SA, Hsia K, Yong FH, et al. Patterns of plasma human immunodeficiency virus type 1 RNA response to highly active antiretroviral therapy in infected children. *J Infect Dis*. 2000;182(6):1769-1773. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11069252>.
18. Starr SE, Fletcher CV, Spector SA, et al. Combination therapy with efavirenz, nelfinavir, and nucleoside reverse-transcriptase inhibitors in children infected with human immunodeficiency virus type 1. Pediatric AIDS Clinical Trials Group 382 Team. *N Engl J Med*. 1999;341(25):1874-1881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10601506>.
19. Starr SE, Fletcher CV, Spector SA, et al. Efavirenz liquid formulation in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(7):659-663. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12237599>.
20. Teglas JP, Quartier P, Treluyer JM, Burgard M, Gregoire V, Blanche S. Tolerance of efavirenz in children. *AIDS*. 2001;15(2):241-243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11216933>.
21. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr*. 2007;45(3):280-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17356468>.

22. Puthanakit T, Tanpaiboon P, Aupibul L, Cressey TR, Sirisanthana V. Plasma efavirenz concentrations and the association with CYP2B6-516G >T polymorphism in HIV-infected Thai children. *Antivir Ther.* 2009;14(3):315-320. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19474465>.
23. Bolton C, Samson P, Capparelli E, Bwakura-Dangarembizi M, Jean-Philippe P, et al. Strong influence of CYP2B6 genotypic polymorphisms on EFV pharmacokinetics in HIV+ children <3 years of age and implications for dosing. Presented at: Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, Georgia.
24. Salem AH, Fletcher CV, Brundage RC. Pharmacometric characterization of efavirenz developmental pharmacokinetics and pharmacogenetics in HIV-infected children. *Antimicrob Agents Chemother.* 2014;58(1):136-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24145522>.
25. Bienczak A, Cook A, Wiesner L, et al. The impact of genetic polymorphisms on the pharmacokinetics of efavirenz in African children. *Br J Clin Pharmacol.* 2016;82(1):185-198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26991336>.
26. Haas DW, Smeaton LM, Shafer RW, et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an adult AIDS clinical trials group study. *J Infect Dis.* 2005;192(11):1931-1942. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16267764>.
27. Soeria-Atmadja S, Osterberg E, Gustafsson LL, et al. Genetic variants in CYP2B6 and CYP2A6 explain interindividual variation in efavirenz plasma concentrations of HIV-infected children with diverse ethnic origin. *PLoS One.* 2017;12(9):e0181316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28886044>.
28. Bolton Moore C, Capparelli EV, Samson P, et al. CYP2B6 genotype-directed dosing is required for optimal efavirenz exposure in children 3-36 months with HIV infection. *AIDS.* 2017;31(8):1129-1136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28323755>.
29. di Iulio J, Fayet A, Arab-Alameddine M, et al. *In vivo* analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics.* 2009;19(4):300-309. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19238117>.
30. Arab-Alameddine M, Di Iulio J, Buclin T, et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. *Clin Pharmacol Ther.* 2009;85(5):485-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19225447>.
31. Mutwa PR, Fillekes Q, Malgaz M, et al. Mid-dosing interval efavirenz plasma concentrations in HIV-1-infected children in Rwanda: treatment efficacy, tolerability, adherence, and the influence of CYP2B6 polymorphisms. *J Acquir Immune Defic Syndr.* 2012;60(4):400-404. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22481606>.
32. Gandhi M, Greenblatt RM, Bacchetti P, et al. A single-nucleotide polymorphism in CYP2B6 leads to >3-fold increases in efavirenz concentrations in plasma and hair among HIV-infected women. *J Infect Dis.* 2012;206(9):1453-1461. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22927450>.
33. Holzinger ER, Grady B, Ritchie MD, et al. Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS clinical trials group protocols implicates several CYP2B6 variants. *Pharmacogenet Genomics.* 2012;22(12):858-867. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23080225>.
34. Capparelli E, Rochon-Duck M, Robbins B, et al. Age-related pharmacokinetics of efavirenz solution. Presented at: Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.
35. Bwakura Dangarembizi M, Samson P, Capparelli EV, et al. Establishing dosing recommendations for efavirenz in HIV/TB-coinfected children younger than 3 years. *J Acquir Immune Defic Syndr.* 2019;81(4):473-480. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31241542>.
36. Bienczak A, Denti P, Cook A, et al. Plasma efavirenz exposure, sex, and age predict virological response in HIV-infected African children. *J Acquir Immune Defic Syndr.* 2016; 73(2):161-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27116047>.
37. Ren Y, Nuttall JJ, Egbers C, et al. High prevalence of subtherapeutic plasma concentrations of efavirenz in children. *J Acquir Immune Defic Syndr.* 2007;45(2):133-136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17417100>.

38. Hirt D, Urien S, Olivier M, et al. Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? *Antimicrob Agents Chemother*. 2009;53(10):4407-4413. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19635964>.
39. Viljoen M, Gous H, Kruger HS, Riddick A, Meyers TM, Rheeders M. Efavirenz plasma concentrations at 1, 3, and 6 months post-antiretroviral therapy initiation in HIV type 1-infected South African children. *AIDS Res Hum Retroviruses*. 2010;26(6):613-619. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20507205>.
40. Fillekes Q, Natukunda E, Balungi J, et al. Pediatric underdosing of efavirenz: a pharmacokinetic study in Uganda. *J Acquir Immune Defic Syndr*. 2011;58(4):392-398. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21926634>.
41. Cressey TR, Aurpibul L, Narkbunnam T, et al. Pharmacological assessment of efavirenz weight-band dosing recommendations in HIV-infected Thai children. *J Acquir Immune Defic Syndr*. 2013;62(1):e27-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23262981>.
42. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther*. 2008;83(2):300-306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17609682>.
43. Larru B, Eby J, Lowenthal ED. Antiretroviral treatment in HIV-1 infected pediatric patients: focus on efavirenz. *Pediatric Health Med Ther*. 2014;5:29-42. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25937791>.
44. Ford N, Shubber Z, Pozniak A, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: A systematic review and meta-analysis of randomized trials. *J Acquir Immune Defic Syndr*. 2015;69(4):422-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25850607>.
45. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis*. 2005;41(11):1648-1653. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16267739>.
46. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*. 2001;15(1):71-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11192870>.
47. Treisman GJ, Kaplin AI. Neurologic and psychiatric complications of antiretroviral agents. *AIDS*. 2002;16(9):1201-1215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12045485>.
48. Wintergerst U, Hoffmann F, Jansson A, et al. Antiviral efficacy, tolerability and pharmacokinetics of efavirenz in an unselected cohort of HIV-infected children. *J Antimicrob Chemother*. 2008;61(6):1336-1339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18343800>.
49. Encore Study Group, Puls R, Amin J, et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naïve adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. *Lancet*. 2014;383(9927):1474-1482. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24522178>.
50. Van de Wijer L, McHaile DN, de Mast Q, et al. Neuropsychiatric symptoms in Tanzanian HIV-infected children receiving long-term efavirenz treatment: a multicentre, cross-sectional, observational study. *Lancet HIV*. 2019;6(4):e250-e258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30770324>.
51. Shubber Z, Calmy A, Andrieux-Meyer I, et al. Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis. *AIDS*. 2013;27(9):1403-1412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23343913>.
52. Mollan KR, Smurzynski M, Eron JJ, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. *Ann Intern Med*. 2014;161(1):1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24979445>.
53. Arenas-Pinto A, Grund B, Sharma S, et al. Risk of suicidal behavior with use of efavirenz: results from the strategic timing of antiretroviral treatment trial. *Clin Infect Dis*. 2018;67(3):420-429. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29538636>.

54. Smith C, Ryom L, Monforte A, et al. Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study. *J Int AIDS Soc.* 2014;17(4 Suppl 3):19512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25394021>.
55. Napoli AA, Wood JJ, Coumbis JJ, Soitkar AM, Seekins DW, Tilson HH. No evident association between efavirenz use and suicidality was identified from a disproportionality analysis using the FAERS database. *J Int AIDS Soc.* 2014;17:19214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25192857>.
56. van Luin M, Gras L, Richter C, et al. Efavirenz dose reduction is safe in patients with high plasma concentrations and may prevent efavirenz discontinuations. *J Acquir Immune Defic Syndr.* 2009;52(2):240-245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19593159>.
57. Acosta EP, Gerber JG, Adult Pharmacology Committee of the AIDS Clinical Trials Group. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Res Hum Retroviruses.* 2002;18(12):825-834. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12201904>.
58. Dickinson L, Amin J, Else L, et al. Comprehensive pharmacokinetic, pharmacodynamic and pharmacogenetic evaluation of once-daily efavirenz 400 and 600 mg in treatment-naïve HIV-infected patients at 96 weeks: results of the ENCORE1 study. *Clinical Pharmacokinet.* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26715213>.
59. Orrell C, Bienczak A, Cohen K, et al. Recommended efavirenz concentration for therapeutic drug monitoring is too high. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, Massachusetts.

# Etravirine (ETR, Intelence) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

Tablets: 25 mg, 100 mg, 200 mg

### Dosing Recommendations

#### Neonate and Infant Dose:

- Etravirine (ETR) is not approved for use in neonates or infants.

#### Child Dose:

- ETR is not approved for use in children aged <2 years. Studies in infants and children aged 2 months to 2 years are under way.

#### Etravirine Dosing Table for Antiretroviral Therapy-Experienced Children and Adolescents Aged 2 to 18 Years and Weighing $\geq 10$ kg

Body Weight	Twice-Daily Dose
10 kg to <20 kg	100 mg
20 kg to <25 kg	125 mg
25 kg to <30 kg	150 mg
$\geq 30$ kg	200 mg

#### Adult Dose for Antiretroviral Therapy-Experienced Patients:

- ETR 200 mg twice daily with food

### Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure

### Special Instructions

- ETR tablets are sensitive to moisture; store the tablets at room temperature in the original container with desiccant.
- Area under the curve of ETR is decreased by about 50% when the drug is taken on an empty stomach. Always administer ETR with food. The type of food does not affect the exposure to ETR.
- Swallowing ETR tablets whole is the preferred means of administration and although the package insert contains instructions for dispersing ETR tablets in water or other liquids, using this administration method generally results in lower ETR exposures than swallowing tablets whole. **Children who receive dispersed ETR tablets should switch to swallowing tablets whole as soon as they are able.**

### Metabolism/Elimination

- ETR is an inducer of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate for CYP3A4, CYP2C9, and CYP2C19.
- ETR is involved in multiple interactions with antiretroviral agents and other drugs (see text below).

#### Etravirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is required when using ETR in patients with mild or moderate

hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

**Etravirine Dosing in Patients with Renal Impairment:**

- No dose adjustment is required when using ETR in patients with renal impairment.

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

- Etravirine (ETR) is associated with multiple drug interactions. A patient's medication profile should be carefully reviewed for potential drug interactions before ETR is administered.
- ETR **should not be administered** with tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs).
- ETR **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine [NVP], efavirenz [EFV], rilpivirine, doravirine).
- Limited data in adults suggest that ETR may reduce the trough concentration of raltegravir (RAL),<sup>1</sup> but no dose adjustment is currently recommended when ETR and RAL are used together. ETR significantly reduces plasma concentrations of dolutegravir (DTG), elvitegravir/cobicistat (EVG/c), and darunavir/cobicistat.<sup>2</sup> DTG should only be used with ETR when these drugs are coadministered with atazanavir/ritonavir, darunavir/ritonavir (DRV/r), or lopinavir/ritonavir. ETR **should not be coadministered** with EVG/c.

**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 to 2 weeks on continued therapy. A history of NNRTI-related rash does not appear to increase the risk of developing rash with ETR. However, patients who have a history of severe rash with prior NNRTI use **should not receive ETR**.
- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme 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 ETR immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and eosinophilia). Clinicians should monitor a patient's clinical status, including levels of liver transaminases, and initiate appropriate therapy when necessary. Continuing to use ETR after the onset of severe rash may result in a life-threatening reaction. People who have a history of severe rash while using NVP or EFV **should not receive ETR**.

**Resistance**

The International AIDS Society-USA (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*

ETR is approved by the Food and Drug Administration for use in antiretroviral therapy (ART)-experienced children and adolescents aged 2 to 18 years.

### Efficacy in Clinical Trials

In the PIANO study,<sup>3</sup> ART-experienced children aged 6 years to <18 years received ETR with a ritonavir (RTV)-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL and 52% had HIV RNA <50 copies/mL. At Week 48, 56% of the participants had HIV RNA <50 copies/mL and a mean increase in their CD4 T lymphocyte (CD4) cell counts of 156 cells/mm<sup>3</sup> 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 ETR-based therapy, 78% of participants achieved HIV RNA <50 copies/mL at a median of 48.4 weeks of follow-up.<sup>4</sup>

### Pharmacokinetics

In a Phase 1 dose-finding study that involved children aged 6 to 17 years, 17 children were given ETR 4 mg/kg twice daily. The study reported that two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose (AUC<sub>0-12h</sub>) and minimum plasma concentration (C<sub>min</sub>)—were lower than the corresponding parameters observed in adults during previous studies.<sup>5</sup> However, a higher dose (ETR 5.2 mg/kg twice daily; maximum 200 mg per dose) yielded acceptable parameters and was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean AUC<sub>0-12h</sub>) remained lower in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either white or black participants. In the PIANO study, children and adolescents with ETR concentrations in the lowest quartile (<2,704 ng·h/mL or C<sub>0h</sub> <145 ng/mL) were less likely to achieve sustained virologic responses (defined as plasma viral loads <50 copies/mL) after 48 weeks of treatment than those with ETR concentrations in the upper three quartiles.<sup>6</sup>

**Table A. Pharmacokinetic Parameters in Children, Adolescents, and Adults Receiving Etravirine Twice Daily**

Population	Mean ETR AUC <sub>0-12h</sub> (ng·h/mL)	Mean ETR C <sub>0h</sub> (ng/mL)
Children Aged 6–11 Years (n = 41)	5,684	377
Adolescents Aged 12–17 Years (n = 60)	4,895	325
Adults (n = 575)	5,506	393

**Key:** AUC<sub>0-12h</sub> = area under the curve for 12 hours post-dose; C<sub>0h</sub> = pre-dose concentration during chronic administration; ETR = etravirine

IMPAACT P1090 examined the PKs and safety of ETR in treatment-experienced children with HIV aged ≥2 years to <6 years.<sup>7</sup> ETR was initially given at a dose of 5.2 mg/kg twice daily to a cohort of six children; however, at this dose the geometric mean ETR AUC<sub>0-12h</sub> values fell below the target range of 60% of the values seen in adults. Subsequent participants were given twice-daily doses of ETR that were determined by weight band: children weighing 10 kg to <20 kg were given 100 mg 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 ETR were achieved at these doses; the geometric mean AUC<sub>0-12h</sub> was 3,504 ng·hr/mL, which was within the target range of 2,713 ng·hr/mL to 6,783 ng·hr/mL (60% to 150% of the AUC<sub>0-12h</sub> value seen in adults). However, considerable intersubject variability was observed, with five of 14 participants (36%) having AUC<sub>0-12h</sub> values that were below the tenth percentile for the adult AUC<sub>0-12h</sub> range (<2,350 ng·hr/mL). The ETR AUC<sub>0-12h</sub> values were significantly lower in children who received dispersed tablets than in children who swallowed intact tablets: 2,841 ng·hr/mL versus 10,721 ng·hr/mL, respectively (*P* < 0.0001). **In light of the**

increased risk of virologic failure that was observed during the PIANO study among children with lower drug exposures, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not generally recommend dispersing the ETR tablet. If ETR is administered in this fashion, the use of therapeutic drug monitoring should be considered.

Five children with HIV aged 1 year to <2 years were also enrolled in P1090. The ETR exposure in these children was lower than the ETR exposure reported in adults; the AUC<sub>0-12h</sub> geometric mean ratio was 0.59 (90% confidence interval, 0.34–1.01). Virologic failure, which was defined as a confirmed viral load  $\geq$ 400 copies/mL, occurred in three of four evaluable children by Week 24.

ETR 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 ETR 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.<sup>8</sup> The PKs of ETR and DRV were also studied in adolescents and young adults who received DRV/r 800 mg/100 mg once daily with either ETR 200 mg twice daily or ETR 400 mg once daily.<sup>9</sup> DRV concentrations were higher when DRV was coadministered with ETR, particularly when the latter was given in doses of 200 mg twice daily. ETR exposures were lower when ETR was given with DRV/r, particularly when ETR was given twice daily; however, the authors noted that these studies had limited sample sizes. While the combination of ETR and DRV/r was effective in a small cohort of adolescents with HIV<sup>10</sup> and in 51% of participants in the PIANO study,<sup>3,6</sup> these data suggest a need for additional data on the PK interactions for ETR and other antiretroviral (ARV) agents in pediatric patients. Most notably, data is needed on regimens that do not include RTV-boosted PIs. Until such data become available, the Panel recommends using ETR as part of a regimen that includes a RTV-boosted PI.

P1090 evaluated the antiviral activity of ETR in treatment-experienced pediatric patients with HIV aged  $\geq$ 2 years to <6 years. At baseline, the mean plasma HIV RNA viral load was approximately 247,000 copies/mL, the median CD4 count was 818 cells/mm<sup>3</sup>, and the mean CD4 percentage was 26%. At Week 24, ETR 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 increase in CD4 count from baseline to Week 24 was 298 cells/mm<sup>3</sup>, and the median increase in CD4 percentage was 5%.

### **Toxicity**

In the PIANO study, rash and diarrhea were the most common adverse drug reactions that were deemed to be possibly related to the use of ETR. Rash (Grade 2 or higher) occurred in 13% of pediatric subjects and emerged at a median of 10 days, lasting a median of 7 days. Rash was observed more frequently in female patients (13 of 64 patients; 20.3%) than in male patients (two of 37 patients; 5.4%). In P1090, adverse drug reactions that were reported for children aged  $\geq$ 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 ETR. 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%).

## **References**

1. Do VT, Higginson RT, Fulco PP. Raltegravir dosage adjustment in HIV-infected patients receiving etravirine. *Am J Health Syst Pharm*. 2011;68(21):2049-2054. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22011983>.
2. Molto J, Curran A, Miranda C, et al. Pharmacokinetics of darunavir/cobicistat and etravirine alone and co-administered in HIV-infected patients. *J Antimicrob Chemother*. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29237008>.
3. Tudor-Williams G, Cahn P, Chokeyhaibulkit K, et al. Etravirine in treatment-experienced, HIV-1-infected children and adolescents: 48-week safety, efficacy and resistance analysis of the phase II PIANO study. *HIV Med*. 2014. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24589294>.

4. Briz V, Palladino C, Navarro M, et al. Etravirine-based highly active antiretroviral therapy in HIV-1-infected paediatric patients. *HIV Med*. 2011;12(7):442-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21395964>.
5. Konigs C, Feiterna-Sperling C, Esposito S, et al. Pharmacokinetics and short-term safety and tolerability of etravirine in treatment-experienced HIV-1-infected children and adolescents. *AIDS*. 2012;26(4):447-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22156961>.
6. Kakuda TN, Brochot A, Green B, et al. Pharmacokinetics and pharmacokinetic/pharmacodynamic relationships of etravirine in HIV-1-infected, treatment-experienced children and adolescents in PIANO. *J Clin Pharmacol*. 2016;56(11):1395-1405. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27060341>.
7. MacBrayne CE, Rutstein R, Yogev R, et al. Etravirine pharmacokinetics in treatment-experienced children ages 1- <6 years. Abstract 465. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/etravirine-pharmacokinetics-treatment-experienced-children-ages-1>.
8. Cressey TR, Yogev R, Wiznia A, et al. Pharmacokinetics of darunavir/ritonavir with etravirine both twice daily in human immunodeficiency virus-infected adolescents and young adults. *J Pediatric Infect Dis Soc*. 2017;6(3):294-296. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27103489>.
9. Larson KB, Cressey TR, Yogev R, et al. Pharmacokinetics of once-daily darunavir/ritonavir with and without etravirine in human immunodeficiency virus-infected children, adolescents, and young adults. *J Pediatric Infect Dis Soc*. 2016;5(2):131-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27199469>.
10. Thuret I, Chaix ML, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS*. 2009;23(17):2364-2366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19823069>.

# Nevirapine (NVP, Viramune) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Oral Suspension:** 10 mg/mL

**Tablets:** Immediate-release 200 mg tablets; extended-release (XR) 100 mg and 400 mg tablets

### Generic Formulations:

- 10 mg/ml suspension
- Immediate-release 200 mg tablets
- XR 400 mg tablets

The oral suspension formulation of brand-name nevirapine (Viramune) is not typically stocked in local pharmacies or hospitals. Have the pharmacy ask their drug wholesaler to order it from the Boehringer-Ingelheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

## Dosing Recommendations

**Note:** Nevirapine (NVP) is often used to prevent perinatal transmission of HIV. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#).

### Child and Adolescent Dose:

- In most situations, NVP is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged <2 years.<sup>a</sup>

### Immediate-Release Tablets and Oral Suspension

#### Gestational Age of 34 to 37 Weeks:

- NVP 4 mg/kg per dose twice daily for the first week, increasing to NVP 6 mg/kg per dose twice daily thereafter (no lead-in dosing).<sup>a</sup>
- This is an **investigational dose** that is not approved by the Food and Drug Administration (FDA).

#### Gestational Age of ≥37 Weeks to Age of <1 Month:

- NVP 6 mg/kg per dose twice daily (no lead-in dosing).<sup>a</sup>
- This is an **investigational dose** that is not approved by the FDA.
- See Special Considerations for Dosing: Neonates and Premature Infants below.

#### Aged ≥1 Month to <8 Years:

- NVP 200 mg per m<sup>2</sup> of body surface area per dose twice daily after lead-in dosing.<sup>a</sup> In children aged ≤2 years, some experts initiate NVP without lead-in dosing (maximum dose of immediate-release tablets is NVP 200 mg twice daily).

## Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis<sup>b</sup>
- Severe systemic hypersensitivity syndrome with potential for multisystem organ involvement and shock

## Special Instructions

- Shake the oral suspension well before administering and store at room temperature.
- NVP can be given without regard to food.
- NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14 day lead-in period, do not increase the dose until rash resolves (see Major Toxicities below).
- Extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If NVP dosing is interrupted for >14 days, NVP should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement below).
- Most cases of NVP-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).

### Aged $\geq 8$ Years:

- NVP 120 mg to 150 mg per  $m^2$  of body surface area per dose twice daily after lead-in dosing<sup>a</sup> (maximum dose of immediate-release tablets is NVP 200 mg twice daily).
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose can be left static to achieve the appropriate mg-per- $m^2$  dose as the child grows, as long as there are no adverse effects (AEs).

### Extended-Release Tablets

#### Aged $\geq 6$ Years:

- Patients aged  $\geq 6$  years who are already taking immediate-release NVP tablets twice daily can be switched to extended-release NVP tablets without lead-in dosing.<sup>a</sup>

### Body Surface Area Dosing for Extended-Release Nevirapine Tablets

Body Surface Area	Once-Daily Dose
0.58 $m^2$ to 0.83 $m^2$	NVP 200 mg (two 100-mg tablets)
0.84 $m^2$ to 1.16 $m^2$	NVP 300 mg (three 100-mg tablets)
$\geq 1.17 m^2$	NVP 400 mg (one 400-mg tablet)

#### Adolescent and Adult Dose:

- NVP 200 mg twice daily or NVP 400 mg with the extended-release tablets once daily after lead-in dosing.<sup>a,b</sup>

### Nevirapine Used in Combination with Lopinavir/Ritonavir:

- A higher dose of lopinavir/ritonavir may be needed in patients who are also receiving NVP (see the [Lopinavir/Ritonavir](#) section for more information).

## Metabolism/Elimination

- NVP is a substrate and inducer of cytochrome P450 (CYP) 3A4 and CYP2B6. More than 80% of a nevirapine dose is eliminated in urine as uridine diphosphate glucuronosyltransferase (UGT)-derived glucuronidated metabolites.

### Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:

- An additional dose of NVP should be given following each dialysis session.

### Nevirapine Dosing in Patients with Hepatic Impairment:

- NVP should not be administered to patients with moderate or severe hepatic impairment.

<sup>a</sup> NVP is usually initiated at a lower dose that is increased in a stepwise fashion. NVP 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 tablet formulation once daily instead of twice daily for the first 14 days of therapy. If there are no rashes or other AEs after 14 days of therapy, increase the dose of NVP to the age-appropriate full dose of the immediate-release tablet formulation administered twice daily. For example, the recommended oral dose for pediatric patients aged  $\geq 1$  month to  $< 8$  years is NVP 200 mg per  $m^2$  of body surface area once daily for the first 14 days, followed by NVP 200 mg per  $m^2$  of body surface area twice daily thereafter. However, in children aged  $\leq 2$  years, some experts initiate NVP 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 the immediate-release tablets, extended-release tablets can be used without the lead-in period. Patients must swallow extended-release tablets whole. They must not be chewed, crushed, or divided. **Patients must never take more than one form of NVP at the same time.** The dose should not exceed NVP 400 mg daily.

<sup>b</sup> Severe, life-threatening, and, in rare cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, have occurred in patients who were taking NVP. These toxicities are less common in children than adults. 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 (HSR). NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.

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

- **Metabolism:** Nevirapine (NVP) induces hepatic cytochrome P450 (CYP), including 3A and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, leading to a 1.5-fold to two-fold increase in NVP clearance. There is potential for multiple drug interactions with NVP. Some genetic polymorphisms of CYP2B6 are associated with increased NVP serum concentrations. CYP2B6 polymorphisms vary among populations and may contribute to differences in NVP exposure. Please see the [Efavirenz](#) section for more information on how polymorphisms can alter enzyme activity.
- NVP should not be coadministered to patients who are receiving atazanavir (ATV) (with or without ritonavir), because NVP substantially decreases ATV exposure.
- NVP increases the metabolism of lopinavir (LPV). A dose adjustment of LPV is recommended when the two drugs are coadministered (see the [Lopinavir/Ritonavir](#) section).
- Before NVP is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

**Major Toxicities**

The following toxicities are seen with continuous dosing regimens, not during single-dose NVP prophylaxis.

- **More common:** Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and elevated hepatic transaminases. NVP should be **discontinued and not restarted** in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated levels of hepatic transaminases. NVP-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until rash resolves. However, the risk of developing NVP resistance with extended lead-in dosing is unknown, and this concern must be weighed against the current antiviral response and a patient's overall ability to tolerate the regimen.
- **Less common (more severe):** Severe, life-threatening, and, in rare cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure. These toxicities are less common in children than adults. 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 (HSR). Risk factors for NVP-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C virus infection, female sex, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 count >250 cells/mm<sup>3</sup> in adult females and >400 cells/mm<sup>3</sup> in adult males). Children with CD4 percentages >15% have a three-fold increase in the risk of rash and hepatotoxicity after initiating NVP.<sup>1</sup> HSRs have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. NVP **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or HSRs.
- **Less common (more severe):** In a cross-sectional study of 201 children with HIV aged 6 to 16 years, 43% of whom had hypertension, the use of NVP was associated with left ventricular hypertrophy (LVH) (adjusted odds ratio 3.14; confidence interval, 1.13–8.72; *P* = 0.03) but not left ventricular diastolic dysfunction.<sup>2</sup> The median duration on antiretroviral therapy (ART) in this cohort was 4.7 years (interquartile range 2.6–6.4 years). The majority of participants (76.6%) were receiving a regimen that included two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor (NNRTI). However, the use of NVP was not associated with LVH in a more recent study by the same authors. LVH has been associated with NVP use in adults.<sup>3,4</sup>

**Resistance**

The International AIDS 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***

NVP is approved by the Food and Drug Administration (FDA) for treatment of HIV in children from infancy (aged  $\geq 15$  days) onward and remains a mainstay of therapy, especially in resource-limited settings.<sup>5-13</sup> The extended-release tablet formulation has been approved by the FDA for use in children aged  $\geq 6$  years.

### ***Efficacy in Clinical Trials***

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to NVP in young children but not in older children. IMPAACT P1060 demonstrated the superiority of LPV/r over NVP in children aged  $< 3$  years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics showed no differences in virologic outcomes between an NNRTI-based regimen (with either NVP or efavirenz [EFV]) and a protease inhibitor (PI)-based regimen in older children with HIV.<sup>14-20</sup>

In infants and children who were previously exposed to a single dose of NVP to prevent perinatal HIV transmission, NVP-based ART is less likely to control viral load than LPV/r-based ART. In P1060, 153 children with HIV and previous exposure to NVP for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine (ZDV) and lamivudine (3TC) plus either NVP or LPV/r. At 24 weeks post-randomization, 24% of children in the NVP arm had experienced virologic failure compared to 7% of children in the LPV/r arm ( $P = 0.0009$ ); virologic failure was defined as  $< 1 \log_{10}$  decrease in HIV RNA during Weeks 12 to 24 or HIV RNA  $> 400$  copies/mL at Week 24. When all primary endpoints were considered, including virologic failure, death, and treatment discontinuation, the PI arm remained superior; 40% of children in the NVP arm met a primary endpoint compared to 22% of children in the LPV/r arm ( $P = 0.027$ ).<sup>17</sup> Similar results were reported in a randomized trial that compared NVP and LPV/r in children aged 6 to 36 months who had not been previously exposed to NVP. This finding suggests that LPV/r-based therapy is superior to NVP-based therapy for infants, regardless of past NVP exposure.<sup>14</sup>

Extended-release NVP tablets (400 mg) were approved by the FDA for use in children aged  $\geq 6$  years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, nonrandomized, crossover trial performed in 85 pediatric participants with HIV. The participants had received at least 18 weeks of immediate-release NVP tablets and had plasma HIV RNA  $< 50$  copies/mL prior to enrollment. Participants were stratified according to age (3 years to  $< 6$  years, 6 years to  $< 12$  years, and 12 years to  $< 18$  years). Participants received immediate-release NVP tablets for 11 weeks. Participants were then treated with NVP extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PKs) were determined.<sup>21</sup> Forty participants who completed the initial part of the study were enrolled in an optional extension phase of the trial, which evaluated the safety and antiviral activity of extended-release NVP tablets through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with extended-release tablets, all 39 participants continued to have plasma HIV RNA  $< 50$  copies/mL.<sup>22</sup>

### ***General Dosing Considerations***

Body surface area has traditionally been used to guide NVP dosing in infants and young children. It is important to avoid underdosing NVP, because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both NVP and EFV. Younger children (those aged  $\leq 8$  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 NVP than older children.<sup>10,11</sup> Because of this, it is recommended that children aged  $< 8$  years receive NVP 200 mg per  $m^2$  of body surface area per dose twice daily (the maximum dose of the immediate-release tablet formulation is NVP 200 mg twice daily) or NVP 400 mg per  $m^2$  of body surface area administered once daily as the extended-release tablet formulation (the maximum dose of the extended-release tablet formulation is NVP 400 mg once daily). For children aged  $\geq 8$  years, the recommended dose of the immediate-release tablet formulation is NVP 120 mg per  $m^2$  of body surface area per dose (with a maximum dose of NVP 200 mg) administered twice daily. The maximum dose of the extended-release tablet formulation is NVP 400 mg once daily for children aged  $\geq 6$  years.

When adjusting the dose for a growing child, the milligram dose need not be decreased (from NVP 200 mg to NVP 120 mg per m<sup>2</sup> of body surface area) as the child reaches 8 years of age; rather, the milligram dose can be left static if there are no adverse effects, and the dose achieves the appropriate mg per m<sup>2</sup> of body surface area dose as the child grows. Some practitioners dose NVP at 150 mg per m<sup>2</sup> of body surface area every 12 hours or NVP 300 mg per m<sup>2</sup> of body surface area once daily if using the extended-release tablets regardless of age, as recommended in the FDA-approved product label. Regardless of age, the maximum dose should never exceed NVP 200 mg twice daily for immediate-release formulations of NVP or NVP 400 mg once daily for extended-release formulations of NVP.

### *Dosing Considerations: Lead-In Requirement*

Underdosing during the lead-in period may have potentially contributed to the poorer performance of NVP 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 have never received NVP. Traditionally, NVP is initiated with an age-appropriate dose that is given only once daily instead of twice daily (NVP 200 mg per m<sup>2</sup> of body surface area in infants aged  $\geq 15$  days and children aged  $< 8$  years, using the immediate-release formulations) during the first 2 weeks of treatment to allow for the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in NVP 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.<sup>23</sup> The CHAPAS-1 trial<sup>24</sup> randomized 211 children to initiate ART with immediate-release NVP without a lead-in dose (participants received an age-appropriate dose twice daily) or with a lead-in dose (participants received an age-appropriate dose once daily) for 2 weeks, followed by standard twice-daily dosing of the immediate-release formulation of NVP. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and there was no difference in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated NVP without a lead-in dose had a statistically significant increase in the incidence of Grade 2 rash, but the majority of participants were able to continue NVP therapy after a brief interruption. Through 96 weeks, a similar percentage of participants in both groups reached the CD4 count and virologic failure endpoints.

After children had been on NVP for 2 weeks, investigators conducted a substudy that examined NVP plasma concentrations 3 to 4 hours after a morning dose of NVP. Among children aged  $< 2$  years, three of 23 children (13%) who initiated at full dose had subtherapeutic NVP 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 age. These findings suggest that a lead-in dose may not be necessary in young patients.<sup>25</sup>

Gopalan et al. analyzed NVP concentrations in 20 children who had a median age of 9 years and who were just starting an NVP-based ARV regimen. Subtherapeutic NVP concentrations, which were defined as trough concentrations  $\leq 4$  mcg/mL, occurred more frequently among children aged  $\leq 8$  years ( $n = 8$ ) than among children aged  $> 8$  years ( $n = 12$ ). Half of the children aged  $\leq 8$  years experienced virologic failure by Week 48.<sup>26</sup> The authors of the study suggested that rapid metabolism of NVP 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 NVP dose escalation strategies in children. Reinitiating half-dose NVP 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 NVP resistance, the half-life of the CYP enzymes,<sup>27</sup> and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends restarting full-dose NVP 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 ARV regimen. Although dosing is available for ZDV and 3TC, data are inadequate for determining the appropriate doses for other ARV drugs. On the basis of PK

modeling, an investigational dose of NVP 6 mg/kg administered twice daily has been proposed for full-term infants who receive HIV diagnoses in the first few days of life.<sup>28-32</sup> However, a dose of NVP 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 NVP 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 NVP 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 NVP >3 mcg/mL in the majority of infants.<sup>33</sup> 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.

## References

1. Kea C, Puthanakit T, et al. Incidence and risk factors for nevirapine related toxicities among HIV-infected Asian children randomized to starting ART at different CD4%. Abstract MOPE240. Presented at: International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. 2011. Rome, Italy.
2. Majonga ED, Rehman AM, Simms V, et al. High prevalence of echocardiographic abnormalities in older HIV-infected children taking antiretroviral therapy. *AIDS*. 2018;32(18):2739-2748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30289814>.
3. Pombo M, Olalla J, Del Arco A, et al. Left ventricular hypertrophy detected by echocardiography in HIV-infected patients. *Eur J Intern Med*. 2013;24(6):558-561. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23664642>.
4. Majonga ED, Rehman AM, McHugh G, et al. Incidence and progression of echocardiographic abnormalities in older children with human immunodeficiency virus and adolescents taking antiretroviral therapy: a prospective cohort study. *Clin Infect Dis*. 2020;70(7):1372-1378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31054255>.
5. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics*. 2007;120(5):e1134-1140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17954553>.
6. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability, and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J*. 2005;24(10):880-885. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16220085>.
7. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
8. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. 2004;350(24):2471-2480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15190139>.
9. Luzuriaga K, Bryson Y, McSherry G, et al. Pharmacokinetics, safety, and activity of nevirapine in human immunodeficiency virus type 1-infected children. *J Infect Dis*. 1996;174(4):713-721. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8843207>.
10. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med*. 1997;336(19):1343-1349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9134874>.
11. Mirochnick M, Clarke DF, Dorenbaum A. Nevirapine: pharmacokinetic considerations in children and pregnant women. *Clinical Pharmacokinetics*. 2000;39(4):281-293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11069214>.
12. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS*. 2003;17(11):1639-1647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12853746>.
13. Wiznia A, Stanley K, Krogstad P, et al. Combination nucleoside analog reverse transcriptase inhibitor(s) plus nevirapine, nelfinavir, or ritonavir in stable antiretroviral therapy-experienced HIV-infected children: week 24 results

- of a randomized controlled trial--PACTG 377. Pediatric AIDS Clinical Trials Group 377 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(12):1113-1121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10954886>.
14. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. 2012;366(25):2380-2389. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716976>.
  15. Babiker A, Castro nee Green H, Compagnucci A, et al. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. *Lancet Infect Dis*. 2011;11(4):273-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21288774>.
  16. Ruel TD, Kakuru A, Ikilezi G, et al. Virologic and immunologic outcomes of HIV-infected Ugandan children randomized to lopinavir/ritonavir or nonnucleoside reverse transcriptase inhibitor therapy. *J Acquir Immune Defic Syndr*. 2014;65(5):535-541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24326597>.
  17. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med*. 2010;363(16):1510-1520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20942667>.
  18. Kanya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;46(2):187-193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17693883>.
  19. Lowenthal ED, Ellenberg JH, Machine E, et al. Association between efavirenz-based compared with nevirapine-based antiretroviral regimens and virological failure in HIV-infected children. *JAMA*. 2013;309(17):1803-1809. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23632724>.
  20. Kekitiinwa A, Spyer M, et al. Virologic response to efavirenz vs. nevirapine-containing ART in the ARROW trial. Conference on Retroviruses and Opportunistic Infections. 2014. Boston, Massachusetts.
  21. Giaquinto C, Anabwani G, Feiterna-Sperling C, et al. Steady-state pharmacokinetics of nevirapine extended-release tablets in HIV-1-infected children and adolescents: an open-label, multiple-dose, cross-over study. *Pediatr Infect Dis J*. 2014;33(7):e173-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24378938>.
  22. Anabwani G, Konigs C, Giaquinto C, et al. Nevirapine extended-release formulation tablets in HIV-1-infected children--long-term follow-up. *Clin Infect Dis*. 2015;61(3):476-479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25917636>.
  23. Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. *J Infect Dis*. 1995;171(3):537-545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7533197>.
  24. Mulenga V, Cook A, Walker AS, et al. Strategies for nevirapine initiation in HIV-infected children taking pediatric fixed-dose combination "baby pills" in Zambia: a randomized controlled trial. *Clin Infect Dis*. 2010;51(9):1081-1089. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20868279>.
  25. Fillekes Q, Mulenga V, Kabamba D, et al. Is nevirapine dose escalation appropriate in young, African, HIV-infected children? *AIDS*. 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23595153>.
  26. Gopalan BP, Mehta K, D'Souza R R, et al. Sub-therapeutic nevirapine concentration during antiretroviral treatment initiation among children living with HIV: implications for therapeutic drug monitoring. *PLoS One*. 2017;12(8):e0183080. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28827836>.
  27. Magnusson MO, Dahl ML, Cederberg J, Karlsson MO, Sandstrom R. Pharmacodynamics of carbamazepine-mediated induction of CYP3A4, CYP1A2, and Pgp as assessed by probe substrates midazolam, caffeine, and digoxin. *Clin Pharmacol Ther*. 2008;84(1):52-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971810>.
  28. Capparelli E, Maswabi K, Rossi S, et al. Nevirapine (NVP) concentrations in HIV-infected newborns receiving therapeutic dosing. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, Massachusetts.
  29. Cressey TR, Yogeve R, Wiznia A, et al. Pharmacokinetics of darunavir/ritonavir with etravirine both twice daily in

human immunodeficiency virus-infected adolescents and young adults. *J Pediatric Infect Dis Soc.* 2017;6(3):294-296. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27103489>.

30. Mirochnick M, Nielsen-Saines K, Pilotto JH, et al. Nevirapine dosing for treatment in the first month of life. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/nevirapine-dosing-treatment-first-month-life-0>.
31. Bolaris MA, Keller MA, Robbins BL, Podany AT, Fletcher CV. Nevirapine plasma concentrations in human immunodeficiency virus-exposed neonates receiving high-dose nevirapine prophylaxis as part of 3-drug regimen. *J Pediatric Infect Dis Soc.* 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26803329>.
32. Cressey TR, Punyawudho B, Le Coeur S, et al. Assessment of nevirapine prophylactic and therapeutic dosing regimens for neonates. *J Acquir Immune Defic Syndr.* 2017;75(5):554-560. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28489732>.
33. Chadwick E, Qin M, Bryson Y, et al. Establishing a treatment dose of nevirapine for full term neonates with perinatal HIV infection: IMPAACT P1115. Presented at: International AIDS Conference. 2016. Durban, South Africa.

# Rilpivirine (RPV, Edurant) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Tablets:** 25 mg

### Fixed-Dose Combination Tablets:

- [Complera] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Odefsey] Emtricitabine 200 mg/rilpivirine 25 mg/tenofovir alafenamide 25 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

## Dosing Recommendations

### Neonate and Infant Dose:

- Rilpivirine (RPV) is not approved for use in neonates or infants.

### Children Aged <12 Years:

- RPV is not approved for use in children aged <12 years (for more information, see the Pharmacokinetics section below).

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

- RPV 25 mg once daily with a meal in antiretroviral therapy (ART)-naive patients who have HIV RNA ≤100,000 copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to RPV and other antiretroviral (ARV) drugs in the new regimen.

### [Complera] Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (TDF)

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

- One tablet once daily with a meal in ART-naive patients with baseline viral loads ≤100,000 copies/mL. One tablet once daily can also be used to replace the current ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Complera.

## Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include drug reaction [or rash] with eosinophilia and systemic symptoms)
- Hepatotoxicity
- Altered adrenocorticotrophic hormone stimulation test of uncertain clinical significance

## Special Instructions

- **Do not start** RPV in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- Patients must be able to take RPV with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- **Do not use** RPV with other non-nucleoside reverse transcriptase inhibitors.
- **Do not use** RPV with proton pump inhibitors (e.g., omeprazole, pantoprazole).
- Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
- H2 receptor antagonists (e.g., cimetidine, famotidine) should only be administered at least 12 hours before or at least 4 hours after RPV.
- Use RPV with caution when coadministering it with a drug that has a known risk of

### [Juluca] Dolutegravir/Rilpivirine

#### Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.
- Not approved for use in children or adolescents (see Simplification of Treatment section below).

### [Odefsey] Emtricitabine/Rilpivirine/Tenofovir Alafenamide (TAF)

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

- One tablet once daily with a meal in ART-naïve patients with HIV RNA ≤ 100,000 copies/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/mL) for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Odefsey.

Torsades de Pointes (for more information, see [CredibleMeds](#)).

### 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.
- RPV 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. **However, RPV should be used with caution in patients with severe renal impairment or end-stage renal disease. These patients should be monitored more frequently for adverse events; renal dysfunction may alter drug absorption, distribution, and metabolism, leading to increased RPV concentrations.**
- **The FDC tablet Complera **should not** be used in patients with creatinine clearance (CrCl) <50 mL/min, and the FDC tablet Odefsey **should not** be used in patients with CrCl <30 mL/min.**
- 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 (RPV) 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 RPV is administered.
- Co-administering RPV with drugs that increase gastric pH may decrease plasma concentrations of RPV.
- Antacids should only be taken at least 2 hours before or at least 4 hours after RPV.
- H<sub>2</sub> receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV.
- Do not use RPV with proton pump inhibitors.
- Rifampin and rifabutin significantly reduce RPV plasma concentrations; coadministration of rifampin and RPV is **contraindicated**. For patients who are concomitantly receiving rifabutin and RPV, the dose of RPV should be doubled to 50 mg once daily and taken with a meal.

- In a cohort of adolescent patients, RPV exposure was two to three times greater when RPV was administered in combination with darunavir/ritonavir (DRV/r) than when RPV was administered alone.<sup>1</sup>

### **Major Toxicities**

- *More common:* Insomnia, headache, rash.
- *Less common (more severe):* Depression or mood changes, suicidal ideation.
- In studies of adults, 7.3% of patients who were treated with RPV showed a change in adrenal function characterized by an abnormal 250-microgram adrenocorticotropic hormone (ACTH) stimulation test (peak cortisol level <18.1 micrograms/dL). In a study of adolescents, six out of 30 patients (20%) developed this abnormality.<sup>2</sup> 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, RPV used in combination with other ARV agents,<sup>2</sup> the fixed-dose combination (FDC) tablet emtricitabine/rilpivirine/tenofovir disoproxil fumarate (FTC/RPV/TDF; Complera),<sup>3</sup> and the FDC tablet emtricitabine/rilpivirine/tenofovir alafenamide (FTC/RPV/TAF; Odefsey) are all approved by the Food and Drug Administration (FDA) for use in persons aged  $\geq 12$  years and weighing  $\geq 35$  kg.<sup>4</sup> The FDC tablet dolutegravir/rilpivirine (DTG/RPV; Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.<sup>5</sup>

#### *Efficacy in Clinical Trials*

An RPV-containing regimen has been compared to an efavirenz (EFV)-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, RPV was shown to be noninferior to EFV. Patients with pretreatment HIV viral loads  $\geq 100,000$  copies/mL who received RPV had higher rates of virologic failure than those who received EFV. These findings resulted in FDA approval for initial therapy with RPV only in patients with HIV viral loads  $\leq 100,000$  copies/mL.<sup>6-9</sup>

A study of ART-naïve adolescents aged 12 to 18 years demonstrated that RPV 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. Among adolescents with baseline viral loads  $\leq 100,000$  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.<sup>10</sup>

Patients must be able to take RPV on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation Odefsey is a small pill and can be useful for certain patients who have difficulty swallowing pills but want to switch from a multipill regimen and who do not have any drug resistance mutations that are associated with the components of Odefsey.

A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years) who acquired HIV perinatally to receive FTC/RPV/TDF (Complera) as part of an off-label medication use program. At the time of enrollment, 12 patients were on a protease inhibitor-based regimen, 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 RPV-based therapy because of adverse events (AEs); no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved and two adolescents with a history of insomnia and abnormal dreams while receiving EFV-based therapy did not report similar problems while receiving RPV-based therapy.<sup>11</sup>

### Pharmacokinetics

The pharmacokinetics (PKs), safety, and efficacy of RPV in children aged <12 years have not been established but are currently being studied in patients aged 6 years to <12 years and weighing  $\geq 17$  kg (*ClinicalTrials.gov* identifier [NCT00799864](https://clinicaltrials.gov/ct2/show/study/NCT00799864)). The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has agreed that the use of RPV may be appropriate in certain children aged <12 years and weighing  $\geq 35$  kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to prescribing RPV in a child in this age and weight group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, PAINT TMC278, investigated a 25-mg dose of RPV given in combination with two NRTIs in ARV-naïve adolescents aged 12 years to <18 years who weighed  $\geq 32$  kg and who had viral loads  $\leq 100,000$  copies/mL.<sup>10</sup> In the dose-finding phase of the study, 11 youth aged >12 years to  $\leq 15$  years and 12 youth aged >15 years to  $\leq 18$  years underwent intensive PK assessment after they took an observed dose of RPV with a meal. PKs were comparable to those in adults; results are listed in the table below.<sup>12</sup>

**Table A. Rilpivirine Pharmacokinetics in Adults and Adolescents Aged 12 Years to <18 Years**

Parameter	Adults	Adolescents Aged 12 Years to <18 Years
Dose	RPV 25 mg once daily	RPV 25 mg once daily
Number of Participants Studied	679	34
<b>AUC<sub>24h</sub> (ng•h/mL)</b>		
Mean $\pm$ SD	2,235 $\pm$ 851	2,424 $\pm$ 1,024
Median (Range)	2,096 (198–7,307)	2,269 (417–5,166)
<b>C<sub>0h</sub> (ng/mL)</b>		
Mean $\pm$ SD	79 $\pm$ 35	85 $\pm$ 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202022s011lbl.pdf).<sup>2</sup>

**Key:** AUC<sub>24h</sub> = area under the curve after 24 hours; C<sub>0h</sub> = plasma concentration just prior to next dose; RPV = rilpivirine; **SD = standard deviation**

In a PK study of youth aged 13 to 23 years who received RPV,<sup>1</sup> RPV exposure was comparable to the exposure observed during the PAINT study in patients who received 25-mg doses of RPV without DRV/r and substantially higher than the exposure observed in those who received 25-mg doses of RPV with DRV/r (RPV area under the curve in this study was 6,740 ng•h/mL). No dose adjustments are currently recommended for adults when RPV is coadministered with DRV/r, where a similar two-fold to three-fold increase in RPV exposure has been reported.<sup>2</sup>

RPV has been reported to have fewer CNS AEs than EFV, and it has been promoted as a replacement ARV drug for some patients who experience CNS effects while receiving EFV. However, there has been concern that the prolonged half-life of EFV might result in residual drug levels that could have an impact on RPV levels. A Thai study evaluated 20 Thai adolescents 4 weeks after they switched from EFV to RPV. The PK parameters of RPV in this study population were comparable to those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks and no patients

discontinued RPV because of AEs.<sup>13</sup>

### *Simplification of Treatment*

Juluca is an FDC tablet that contains DTG 50 mg and RPV 25 mg. The results from two trials in adults (SWORD-1 and SWORD-2) supported FDA approval of DTG/RPV as a complete regimen for treatment simplification or maintenance therapy in certain patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations that are associated with DTG or RPV. The participants were randomized to receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.<sup>14</sup> After 52 weeks, the participants who had been randomized to continue their suppressive ARV regimen were switched to DTG/RPV. At 100 weeks of treatment, 86% of the early switch patients and 93% of the late switch patients remained virologically suppressed.<sup>15</sup> More AEs were reported and more AEs led to discontinuation in the DTG/RPV arm during the comparative randomized phase. In a subgroup of SWORD study patients whose original ARV regimen contained TDF, small but statistically significant increases in hip and spine bone mineral density were observed.<sup>16</sup> Although DTG/RPV as Juluca is not approved for use in adolescents, the doses of both component drugs that make up Juluca are approved for use in adolescents. This product may be appropriate for certain adolescents; however, because the strategy of treatment simplification has not been evaluated in adolescents, who may have difficulties adhering to therapy, the Panel **does not recommend** using Juluca in adolescents and children until more data are available.

### *Long-Acting, Injectable Rilpivirine*

A long-acting, injectable formulation of RPV is under development as a treatment for adult patients; this formulation is designed to be administered concurrently with a cabotegravir long-acting injectable.<sup>17-19</sup> [IMPAACT study 2017](#), More Options for Children and Adolescents (MOCHA), is currently enrolling participants to evaluate the safety, tolerability, acceptability, and PKs of this injectable regimen in adolescents.

### *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 Grade 3 and 4 depressive disorders was 5.6% (two of 36 participants).<sup>2</sup>

Six out of 30 adolescents (20%) with a normal ACTH stimulation test at baseline developed an abnormal test during the trial. There were no serious AEs, deaths, or treatment discontinuations that were attributed to adrenal insufficiency. The clinical significance of abnormal ACTH stimulation tests is not known, but this finding warrants further evaluation.<sup>2</sup>

## References

1. Foca M, Yogev R, Wiznia A, et al. Rilpivirine pharmacokinetics without and with darunavir/ritonavir once daily in adolescents and young adults. *Pediatr Infect Dis J*. 2016;35(9):e271-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27187753>.
2. Rilpivirine [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/202022s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202022s013lbl.pdf).
3. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/202123s031lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202123s031lbl.pdf).
4. Lopinavir/ritonavir (Kaletra) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/021251s058,021906s053lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021251s058,021906s053lbl.pdf).
5. Dolutegravir/rilpivirine (Juluca) [package insert]. Food and Drug Administration. 2019. Available at: <https://www>.

6. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a Phase 3, randomised, non-inferiority trial. *Lancet*. 2011;378(9787):229-237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21763935>.
7. Cohen CJ, Molina JM, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. *J Acquir Immune Defic Syndr*. 2012;60(1):33-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22343174>.
8. Cohen CJ, Molina JM, Casseti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS*. 2013;27(6):939-950. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23211772>.
9. Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a Phase 3 randomised double-blind active-controlled trial. *Lancet*. 2011;378(9787):238-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21763936>.
10. Lombaard J, Bunupuradah T, Flynn PM, et al. Rilpivirine as a treatment for HIV-infected antiretroviral-naive adolescents: Week 48 safety, efficacy, virology and pharmacokinetics. *Pediatr Infect Dis J*. 2016; 35(11):1215-1221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27294305>.
11. Falcon-Neyra L, Palladino C, Navarro Gomez ML, et al. Off-label use of rilpivirine in combination with emtricitabine and tenofovir in HIV-1-infected pediatric patients: a multicenter study. *Medicine (Baltimore)*. 2016;95(24):e3842. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27310962>.
12. Crauwels H, Hoogstoel A, Vanveggel S, et al. Rilpivirine pharmacokinetics in HIV-1-infected adolescents: a substudy of PAINT (Phase II trial). Presented at: Conference on Retroviruses and Opportunistic Infections. 2014. Boston, MA. Available at: <http://www.croiconference.org/sessions/rilpivirine-pharmacokinetics-hiv-1-infected-adolescents-substudy-paint-phase-ii-trial>.
13. Jantarabenjakul W, Anugulruengkitt S, Kasipong N, et al. Pharmacokinetics of rilpivirine and 24-week outcomes after switching from efavirenz in virologically-suppressed HIV-1-infected adolescents. *Antivir Ther*. 2017; 23(3):259-265. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28994660>.
14. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet*. 2018;391(10123):839-849. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29310899>.
15. About M, Orkin C, Podzamczar D, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. *Lancet HIV*. 2019;6(9):e576-e587. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31307948>.
16. McComsey G, Gonzalez-Garcia J, Lupo S, et al. Sub-study 202094 of SWORD 1 & SWORD 2: switch from TDF containing regimen to DTG+RPV improves bone mineral density and bone turnover markers over 48 weeks. Presented at: IAS Conference on HIV Science. 2017. Paris, France. Available at: <http://programme.ias2017.org/Abstract/Abstract/5743>.
17. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017;390(10101):1499-1510. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28750935>.
18. Swindells S, Andrade-Villanueva J, Richmond G, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: atlas week 48 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-maintenance-therapy-atlas-week-48-results>.
19. Orkin C, Arasteh K, Hernandez-Mora M, et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: flair week 48 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/long-acting-cabotegravir-rilpivirine-hiv-maintenance-flair-week-48-results>.

## **Protease Inhibitors (PIs)**

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Lopinavir/Ritonavir (LPV/r, Kaletra)

# Atazanavir (ATV, Reyataz) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Powder Packet:** 50 mg/packet

**Capsules:** 150 mg, 200 mg, and 300 mg

### Generic Formulations

- 150 mg, 200 mg, and 300 mg capsules

### Fixed-Dose Combination Tablets:

- [Evotaz] Atazanavir 300 mg/cobicistat 150 mg

**Capsules and powder packets are not interchangeable.**

## Dosing Recommendations

### Neonate Dose:

- Atazanavir (ATV) is not approved for use in neonates and infants aged <3 months. ATV **should not be administered** to neonates due to risks associated with hyperbilirubinemia (e.g., **bilirubin-induced neurologic dysfunction**).

### Infant and Child Dose

#### *Powder Formulation of Atazanavir:<sup>a</sup>*

- The powder formulation of ATV must be administered with ritonavir (RTV).
- The powder formulation is not approved for use in infants aged <3 months or weighing <5 kg.

#### **Atazanavir Powder Dosing Table for Infants and Children Aged ≥3 Months and Weighing ≥5 kg<sup>a</sup>**

Weight	Once-Daily Dose
5 kg to <15 kg	ATV 200 mg (four packets) plus RTV 80 mg (1 mL oral solution), with food
15 kg to <25 kg <sup>b</sup>	ATV 250 mg (five packets) plus RTV 80 mg (1 mL oral solution), both with food

#### *Capsule Formulation of Atazanavir:<sup>a</sup>*

- ATV capsules are not approved for use in children aged <6 years or weighing <15 kg.

#### **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	ATV/r <sup>c</sup> 200 mg/100 mg, both with food
≥35 kg	ATV/r <sup>c</sup> 300 mg/100 mg, both with food

## Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Nephrolithiasis
- Increased serum transaminases
- Hyperlipidemia (occurs primarily with RTV boosting)

## Special Instructions

- Administer ATV with food to enhance absorption.
- Capsules and powder packets **are not interchangeable**.
- Do not open capsules.
- Because ATV can prolong the PR interval of the electrocardiogram, use ATV with caution in patients with 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).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, dosing adjustments may be indicated (see the Drug Interactions section in the [ATV package insert](#)).
- The plasma concentration, and therefore the therapeutic effect, of ATV can be expected to decrease substantially when ATV is coadministered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naive patients who are receiving any PPI should receive a dose of that PPI that is equivalent

## ART-Naive Patients Who Are Unable to Tolerate Ritonavir

*Child and Adolescent (Aged  $\geq 13$  Years and Weighing  $\geq 40$  kg) and Adult Dose:*

- ATV 400 mg (capsule formulation only) once daily with food
- ATV powder is not an option, since it must be administered with RTV.
- For the capsule formulation, while the Food and Drug Administration (FDA) does not recommend the use of unboosted ATV in children aged  $<13$  years, adolescents aged  $\geq 13$  years and weighing  $\geq 40$  kg may be prescribed unboosted ATV if they are not concurrently taking tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF).
- In order to achieve target drug concentrations, adolescents may require doses of ATV that are higher than those recommended for use in adults (see Pediatric Use below).
- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **does not recommend** the use of unboosted ATV.

## ART-Naive and ART-Experienced Patients

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- Atazanavir/ritonavir (ATV/r) 300 mg/100 mg once daily with food<sup>d</sup>
- Atazanavir/cobicistat (ATV/c) 300 mg/150 mg once daily with food, administered as single agents simultaneously or as the coformulated drug Evotaz<sup>e</sup>
- **Both ATV/r and ATV/c must be used in combination with other antiretroviral drugs.**

### [Evotaz] Atazanavir/Cobicistat

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily with food

to no more than a 20-mg dose of omeprazole. PPIs should be taken approximately 12 hours before taking boosted ATV. Coadministration of ATV with PPIs **is not recommended** in ART-experienced patients.

- Patients with hepatitis B virus or hepatitis C virus infections and patients who had marked elevations in transaminase levels before treatment may have an increased risk of further elevations in transaminase levels or hepatic decompensation.
- ATV oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet of oral powder contains 35 mg of phenylalanine.

### Powder Administration:

- Mix ATV oral powder with at least 1 tablespoon of soft food (e.g., applesauce, yogurt). Oral powder mixed with a beverage (at least 30 mL of milk or water) may be used for older infants who can drink from a cup. For young infants (aged  $<6$  months) who cannot eat solid food or drink from a cup, oral powder should be mixed with at least 10 mL of infant formula and given using an oral dosing syringe.
- Administer RTV immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.

### Metabolism/Elimination

- ATV is a substrate and inhibitor of cytochrome P450 (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronyl transferase 1A1.

### Atazanavir Dosing in Patients with Hepatic Impairment:

- ATV should be used with caution in patients with mild or moderate hepatic impairment. Consult the manufacturer's prescribing information for the dose adjustment in patients with moderate impairment.
- ATV **should not be used** in patients with severe hepatic impairment.

### Atazanavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required for patients with renal impairment.
- ATV should not be given to ART-experienced patients with end-stage renal disease who are on hemodialysis.

- <sup>a</sup> mg/kg dosing is higher for the ATV powder packets than for the capsules. In P1020A, children of similar age and size who were taking ATV powder had lower exposures than those who were taking ATV capsules.
- <sup>b</sup> Children weighing  $\geq 25$  kg who cannot swallow ATV capsules may receive ATV 300 mg oral powder (six packets) plus RTV 100 mg oral solution, both administered once daily with food.
- <sup>c</sup> Either RTV capsules or RTV oral solution can be used.
- <sup>d</sup> Adult patients who cannot swallow capsules may take ATV oral powder once daily with food using the adult dose for the capsules. ATV oral powder should be administered with RTV.
- <sup>e</sup> See the [Cobicistat section](#) for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat (COBI) and the combination of COBI and TDF.

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

- **Metabolism:** Atazanavir (ATV) is both a substrate and an inhibitor of the cytochrome P450 (CYP) 3A4 enzyme system and has significant interactions with drugs that are highly dependent on CYP3A4 for metabolism. ATV also competitively inhibits CYP1A2 and CYP2C9. ATV is a weak inhibitor of CYP2C8. ATV inhibits the glucuronidation enzyme uridine diphosphate glucuronyl transferase (UGT1A1). Because there is potential for multiple drug interactions with ATV, a patient's medication profile should be carefully reviewed for potential drug interactions before administering ATV.
- **Nucleoside reverse transcriptase inhibitors (NRTIs):** Tenofovir disoproxil fumarate (TDF) decreases ATV plasma concentrations. Only atazanavir/ritonavir (ATV/r) **or atazanavir/cobicistat (ATV/c)** should be used in combination with TDF. The effect of tenofovir alafenamide (TAF) on unboosted ATV is unknown; thus, only ATV/r **or ATV/c** should be used with TAF.
- **Non-nucleoside reverse transcriptase inhibitors:** Efavirenz (EFV), etravirine (ETR), and nevirapine (NVP) decrease ATV plasma concentrations significantly. NVP and ETR **should not be administered** to patients who are receiving ATV (with or without a booster). **Although the combination of EFV and ATV/r is not commonly used in clinical practice,** EFV may be used in combination with ritonavir (RTV)-boosted ATV 400 mg in antiretroviral therapy (ART)-naive patients. ATV/r should be taken with food, and EFV should be taken on an empty stomach, preferably at bedtime. **Coadministering ATV/r and EFV in ART-experienced patients is not recommended, as this combination is expected to result in suboptimal ATV exposure in these patients.**
- **Integrase strand transfer inhibitors:** ATV is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir (RAL). This interaction may not be clinically significant.
- **Absorption:** ATV absorption is dependent on low gastric pH. The dose for ATV should be adjusted when it is administered with medications that alter gastric pH. Guidelines for the appropriate doses of ATV to use with antacids, H2 receptor antagonists, and proton-pump inhibitors in adults are complex and can be found on the [package insert for ATV](#). No information is available on the appropriate doses of ATV to use in children when the drug is coadministered with medications that alter gastric pH.
- Coadministering cobicistat (COBI), a CYP3A4 inhibitor, and medications that are metabolized by CYP3A4 may increase the plasma concentrations of these medications. This may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions) that are associated with the concomitant medications. Coadministration of COBI, ATV, and CYP3A4 inducers may lead to lower exposures of COBI and ATV, a loss of efficacy of ATV, and possible development of resistance.<sup>1</sup> Coadministering COBI and ATV with some antiretroviral (ARV) agents (e.g., with ETR, with EFV in ART-experienced patients, or with another ARV drug that requires pharmacokinetic [PK] enhancement, such as another protease inhibitor [PI] or elvitegravir) may result in decreased plasma concentrations of that agent, leading to loss of therapeutic effect and the development of resistance.

## Major Toxicities

- *More common:* Indirect hyperbilirubinemia that can result in jaundice or icterus but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesia.
- *Less common:* Prolongation of the electrocardiogram PR interval. Abnormalities in atrioventricular (AV) conduction are generally limited to first-degree AV block, but 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 use of ATV/r is associated with lipid abnormalities, but to a lesser extent than with other boosted PIs.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of 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 ATV drug crystals in the renal parenchyma have occurred. Nephrolithiasis and cholelithiasis have been reported. Hepatotoxicity (patients with hepatitis B virus or hepatitis C virus infections are at increased risk of hepatotoxicity).

## Resistance

The International Antiviral Society-USA (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

ATV is approved by the Food and Drug Administration (FDA) for use in infants (aged  $\geq 3$  months and weighing  $\geq 5$  kg), children, and adolescents. **Although the FDA has not approved the use of ATV coformulated with COBI (as Evotaz) in pediatric patients, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends use of this FDC in pediatric patients weighing  $\geq 35$  kg based on FDA approval of the component drugs.**

### Efficacy

Studies in ART-naïve adults have shown that ATV/r is as effective as EFV and lopinavir/ritonavir (LPV/r) when these drugs are administered with two NRTIs.<sup>2-5</sup> In ACTG A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or RAL, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, the regimen that contained ATV/r was discontinued more frequently than the other regimens due to toxicity, most often hyperbilirubinemia or gastrointestinal complaints.<sup>6</sup>

P1020 enrolled 195 ART-naïve and ART-experienced patients with HIV aged 3 months to 21 years. Capsule and powder formulations of ATV given with and without RTV boosting were investigated in this open-label study; area under the curve (AUC) targeting was used to direct dose finding. Of the 195 patients enrolled, 142 patients received ATV-based treatment at the final recommended dose. Among these patients, 58% were ART-naïve. At Week 48, 69.5% of the ART-naïve patients and 43.3% of the ART-experienced patients had HIV viral loads  $\leq 400$  copies/mL.<sup>7,8</sup>

Two open-label clinical trials in infants and children, PRINCE I and PRINCE II, studied a powder formulation of ATV that was administered once daily and boosted with liquid RTV.<sup>9-11</sup> One hundred and thirty-four infants and children aged  $\geq 3$  months and weighing between 5 kg and 35 kg were evaluated. Using a modified intent-to-treat analysis, 28 of 52 ARV-naïve patients (54%) and 41 of 82 ART-experienced patients (50%) had HIV RNA  $< 50$  copies/mL at Week 48. The median increase from baseline in absolute CD4 T lymphocyte cell count at 48 weeks of therapy was 215 cells/mm<sup>3</sup> (a 6% increase) in ARV-naïve patients and 133 cells/mm<sup>3</sup> (a 4% increase) in ARV-experienced patients.

Oral Capsule

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of RTV boosting, ATV can achieve protocol-defined PK targets—but only when used at higher doses (on a mg/kg body weight or mg per m<sup>2</sup> of body surface area basis) than the doses that are currently recommended in adults. In IMPAACT/PACTG 1020A, children aged >6 years to <13 years required 520 mg per m<sup>2</sup> of body surface area per day of the ATV capsule formulation to achieve PK targets.<sup>8</sup> Unboosted ATV at this dose was well tolerated in those aged <13 years who were able to swallow capsules.<sup>12</sup> The approved dose for adults is ATV 400 mg once daily without RTV boosting; however, adolescents aged >13 years required a dose of ATV 620 mg per m<sup>2</sup> of body surface area per day.<sup>8</sup> 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<sub>max</sub>) was higher and the minimum plasma concentration (C<sub>min</sub>) was lower in the unboosted arms. Median doses of ATV, both with and without RTV boosting, from IMPAACT/PACTG 1020A are outlined in the table below. When administering unboosted ATV to pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate ATV plasma concentrations have been achieved. A minimum target trough concentration for ATV is 150 ng/mL.<sup>13</sup> Higher target trough concentrations may be required in PI-experienced patients. IMPAACT P1058, a study of unboosted ATV PKs in ART-experienced children, concluded that once-daily ATV 400 mg provided suboptimal exposure and that administering higher, unboosted doses or splitting the daily dose into twice-daily doses warranted investigation in ART-experienced children, adolescents, and young adults.<sup>14</sup>

**Table A. Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A**

Age Range	ATV Given with RTV	ATV Median Dose (mg/m <sup>2</sup> ) <sup>a</sup>	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

<sup>a</sup> 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:** AUC = area under the curve; ATV = atazanavir; PK = pharmacokinetic; RTV = ritonavir; TDM = therapeutic drug monitoring

In the report of the IMPAACT/ PACTG P1020A data, ATV satisfied PK criteria at a dose of 205 mg per m<sup>2</sup> of body surface area in pediatric subjects when administered with RTV.<sup>15</sup> A study of a model-based approach that used ATV concentration-time data from three adult studies and one pediatric study (P1020A),<sup>16</sup> along with subsequent additional adjusted modeling,<sup>17</sup> informed the use of the following weight-based ATV/r doses that are listed in the current, FDA-approved product label for children aged ≥6 years to <18 years:

- Weighing 15 kg to <35 kg: ATV/r 200 mg/100 mg
- Weighing ≥35 kg: ATV/r 300 mg/100 mg

Cobicistat as a Pharmacokinetic Enhancer

**COBI (as Tybost) is approved by the FDA at the 150-mg dose for use with ATV 300 mg in children and adolescents weighing ≥35 kg.** A study of 14 adolescents, aged 12 to 18 years, showed that COBI is a safe and effective PK enhancer when used in combination with ATV and two NRTIs in adolescent patients.<sup>18</sup> PK findings from this study are summarized in Table B below.

**Table B. Pharmacokinetic Parameters for Atazanavir Administered with Cobicistat (as Tybost) in Pediatric Patients Aged 12 to 18 Years and Adults**

PK Parameters <sup>a</sup>	ATV		COBI	
	Pediatric Patients (n = 12)	Adult Patients (n = 30)	Pediatric Patients (n = 12)	Adult Patients (n = 30)
<b>AUC<sub>tau</sub></b> µg·h/mL Geometric Mean (CV%)	49.48 (49.1)	39.96 (52.1)	12.11 (44.7)	9.65 (41.8)
<b>C<sub>max</sub></b> µg/mL Geometric Mean (CV%)	4.32 (49.9)	3.54 (45.8)	1.28 (31.7)	1.28 (35.6)
<b>C<sub>tau</sub></b> µg/mL Geometric Mean (CV%)	0.91 (96.4)	0.58 (84.7)	0.09 (156.2)	0.04 (112.7)

<sup>a</sup> The information in this table comes from the Tybost package insert.<sup>10</sup>

**Key:** ATV = atazanavir; AUC<sub>tau</sub> = area under the concentration time curve over the dosing interval; C<sub>max</sub> = maximum serum concentration; COBI = cobicistat; C<sub>tau</sub> = trough serum concentration at the end of the dosing interval; CV = coefficient of variation; PK = pharmacokinetic

### Oral Powder

The unboosted ATV powder arms in IMPAACT/ PACTG P1020A were closed because participants were unable to achieve target exposures. For the IMPAACT/PACTG P1020A trial, AUC targets (30,000 ng·hr/mL to 90,000 ng·hr/mL) were established based on exposures in adults in early studies of unboosted ATV. In IMPAACT/PACTG P1020A, children aged 3 months to 2 years who were in the boosted ATV powder cohorts and who received a daily dose of ATV 310 mg per m<sup>2</sup> of body surface area achieved average ATV exposures that approached, but did not meet, protocol targets. Variability in exposures was high, especially among the very young children in this age range.<sup>8</sup>

Assessment of the PKs, safety, tolerability, and virologic response of ATV oral powder for FDA approval was based on data from two open-label, multicenter clinical trials:

- PRINCE I, which enrolled pediatric patients aged 3 months to <6 years;<sup>9</sup> and
- PRINCE II, which enrolled pediatric patients aged 3 months to <11 years.<sup>10</sup>

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 ATV and two NRTIs. Children received an oral solution that contained ATV and RTV. Doses were assigned according to the child's weight:

- Weighing 5 kg to <10 kg: ATV 150 mg or ATV 200 mg and RTV 80 mg
- Weighing 10 kg to <15 kg: ATV 200 mg and RTV 80 mg
- Weighing 15 kg to <25 kg: ATV 250 mg and RTV 80 mg
- Weighing 25 kg to <35 kg: ATV 300 mg and RTV 100 mg

No new safety concerns were identified during these trials. Table C lists the PK parameters that were measured during the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses.

**Table C. Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE I and II) versus Capsules in Young Adults and Adults**

PK Parameters	PRINCE Trial <sup>a</sup> ATV/r	PRINCE Trial <sup>a</sup> ATV/r	PRINCE Trial <sup>a</sup> ATV/r	PRINCE Trial <sup>a</sup> ATV/r	PRINCE Trial <sup>a</sup> ATV/r	Young Adult Study <sup>b</sup>	Adult Study
	Dose: 150 mg/80 mg Weighing: 5 kg to <10 kg	Dose: 200 mg/80 mg Weighing: 5 kg to <10 kg	Dose: 200 mg/80 mg Weighing: 10 kg to <15 kg	Dose: 250 mg/80 mg Weighing: 15 kg to <25 kg	Dose: 300 mg/100 mg Weighing: ≥25 kg to <35 kg		
AUC ng·h/mL Mean <sup>c</sup> (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 <sub>24h</sub> ng/mL Mean <sup>c</sup> (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]

<sup>a</sup> This information comes from the Reyataz package insert.<sup>10</sup>

<sup>b</sup> The young adults were also receiving TDF.<sup>7</sup>

<sup>c</sup> Means are geometric means.

**Key:** 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 ATV 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, ATV 300 mg powder (six packets) plus RTV 100 mg oral solution, both administered once daily with food, may be used. ATV capsules should be used for children who can swallow pills. Bioavailability is higher for the capsules than for the powder; therefore, a lower mg/kg dose is recommended when using capsules. Opened capsules have not been studied and should not be used.

### Toxicity

Nine percent of patients enrolled in the IMPAACT/PACTG 1020A trial had a total bilirubin ≥5.1 times the upper limit of normal.<sup>12</sup> Nine percent of patients enrolled in the PRINCE studies had a total bilirubin ≥2.6 times the upper limit of normal.<sup>9,11</sup> The most common laboratory abnormality during the PRINCE trials was elevated amylase levels, which occurred in 33% of patients.<sup>10</sup> 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.<sup>9,11</sup> In IMPAACT/PACTG P1020A, three children (3%) had QTC prolongations >470 msec; two of these children came off study, and all were asymptomatic.

## References

1. Tybost [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/203094s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203094s014lbl.pdf).
2. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr*. 2004;36(5):1011-1019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15247553>.
3. Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily antiretroviral therapy for HIV-1 infection: results from the STARTMRK005 trial. *JAMA*. 2010;304(12):1511-1521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20612100>.

daily highly active antiretroviral therapy regimens in antiretroviral-naïve patients. *J Acquir Immune Defic Syndr*. 2008;47(2):161-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971713>.

4. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646-655. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18722869>.
5. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr*. 2010;53(3):323-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20032785>.
6. Lennox JL, Landovitz RJ, Ribaldo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25285539>.
7. Kiser JJ, Fletcher CV, Flynn PM, et al. Pharmacokinetics of antiretroviral regimens containing tenofovir disoproxil fumarate and atazanavir-ritonavir in adolescents and young adults with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2008;52(2):631-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025112>.
8. Kiser JJ, Rutstein RM, Samson P, et al. Atazanavir and atazanavir/ritonavir pharmacokinetics in HIV-infected infants, children, and adolescents. *AIDS*. 2011;25(12):1489-1496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21610486>.
9. Strehlau R, Donati AP, Arce PM, et al. PRINCE-1: safety and efficacy of atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naïve and -experienced infants and children aged  $\geq 3$  months to  $< 6$  years. *J Int AIDS Soc*. 2015;18:19467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26066346>.
10. Atazanavir [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/021567s042.206352s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021567s042.206352s007lbl.pdf).
11. Cotton MF, Liberty A, Torres-Escobar I, et al. Safety and efficacy of atazanavir powder and ritonavir in HIV-1-infected infants and children from 3 months to  $< 11$  years of age: the PRINCE-2 study. *Pediatr Infect Dis J*. 2018;37(6):e149-e156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29206747>.
12. Rutstein RM, Samson P, Fenton T, et al. Long-term safety and efficacy of atazanavir-based therapy in HIV-infected infants, children and adolescents: the pediatric AIDS clinical trials group protocol 1020A. *Pediatr Infect Dis J*. 2015;34:162-167. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25232777>.
13. Gonzalez de Requena D, Bonora S, Canta F, et al. Atazanavir Ctrough is associated with efficacy and safety at 24 weeks: definition of therapeutic range. Abstract 60. Presented at: International Workshop on Clinical Pharmacology of HIV Therapy. 2005. Quebec City, Canada.
14. Cressey TR, Hazra R, Wiznia A, et al. Pharmacokinetics of unboosted atazanavir in treatment-experienced HIV-infected children, adolescents and young adults. *Pediatr Infect Dis J*. 2016;35(12):1333-1335. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27583590>.
15. Marzolini C, Gibbons S, Khoo S, Back D. Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. *J Antimicrob Chemother*. 2016;71(7):1755-1758. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26945713>.
16. Hong Y, Kowalski KG, Zhang J, et al. Model-based approach for optimization of atazanavir dose recommendations for HIV-infected pediatric patients. *Antimicrob Agents Chemother*. 2011;55(12):5746-5752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21930880>.
17. Sevinsky H, Cirincione B, Raybon J. Challenges in developing a population PK model describing the PK of atazanavir and supporting dose selection in HIV infected pediatric subjects. Presented at: The Seventh American Conference on Pharmacometrics. 2016. Bellevue, Washington.
18. McFarland EJ, Heresi GP, Batra J, et al. Pharmacokinetics, safety, and efficacy of ATV or DRV with COBI in adolescents. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.

## Darunavir (DRV, Prezista) (Last updated April 14, 2020; last reviewed April 14, 2020)

### 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 10 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

**Note:** Darunavir (DRV) should not be used without a pharmacokinetic (PK) enhancer (boosting agent). Ritonavir (RTV) may be used as the boosting agent in children and adults. **Cobicistat (COBI) may be used as a boosting agent with DRV in children weighing  $\geq 40$  kg and in adults.**

#### Neonate/Infant Dose:

- DRV is not approved for use in neonates/infants.

#### Child Dose

*Aged <3 Years:*

- **Do not use DRV in children aged <3 years or weighing  $\leq 10$  kg.** In juvenile rats, DRV caused convulsions and death, and these events have been attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

*Aged  $\geq 3$  Years to <12 Years:*

- Dosing recommendations in the table below are for children aged  $\geq 3$  years to <12 years and weighing  $\geq 10$  kg who are antiretroviral therapy (ART)-naïve or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with DRV resistance.

### 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 DRV is not generally recommended for use in children aged <12 years or weighing <40 kg. Dosing estimates for these patients were based on limited data, and there is limited clinical experience with this dosing schedule in this age group.
- Once-daily DRV **should not be used** if any one of the following resistance-associated mutations are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.
- DRV must be administered with food, which increases DRV plasma concentrations by 30%.
- DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies.
- Pediatric dosing requires coadministration of tablets with different strengths to achieve the

**Twice Daily Darunavir and Ritonavir Doses for Children Aged 3 Years to <12 Years and Weighing  $\geq 10$  kg**

Weight	Dose (Twice Daily with Food) <sup>a</sup>
10 kg to <11 kg <sup>b</sup>	DRV 200 mg (2.0 mL) plus RTV 32 mg (0.4 mL)
11 kg to <12 kg <sup>b</sup>	DRV 220 mg (2.2 mL) plus RTV 32 mg (0.4 mL) <sup>c</sup>
12 kg to <13 kg <sup>b</sup>	DRV 240 mg (2.4 mL) plus RTV 40 mg (0.5 mL) <sup>c</sup>
13 kg to <14 kg <sup>b</sup>	DRV 260 mg (2.6 mL) plus RTV 40 mg (0.5 mL) <sup>c</sup>
14 kg to <15 kg	DRV 280 mg (2.8 mL) plus RTV 48 mg (0.6 mL) <sup>c</sup>
15 kg to <30 kg	DRV 375 mg (combination of tablets or 3.8 mL) <sup>d</sup> plus RTV 48 mg (0.6 mL) <sup>d</sup>
30 kg to <40 kg	DRV 450 mg (combination of tablets or 4.6 mL) <sup>d,e</sup> plus RTV (100 mg tablet or powder or 1.25 mL) <sup>b</sup>
$\geq 40$ kg	DRV 600 mg (tablet or 6 mL) plus RTV 100 mg (tablet or 1.25 mL)

**Child and Adolescent (Aged  $\geq 12$  Years and Weighing  $\geq 30$  to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With or Without at Least One Mutation Associated With Darunavir Resistance:**

- DRV 450 mg (using a combination of tablets) plus RTV 100 mg, both **twice daily with food**

**Child and Adolescent (Aged  $\geq 12$  years and Weighing  $\geq 40$  kg)<sup>e</sup> and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated With Darunavir Resistance:**

- DRV 800 mg (using a tablet or combination of tablets) plus RTV 100 mg **once daily with food**

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance:**

- DRV 800 mg (tablet) plus COBI<sup>f</sup> 150 mg (tablet) or the coformulation Prezcofix **once daily with food**

**Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Experienced Patients with at Least One Mutation Associated with Darunavir Resistance:**

- DRV 600 mg plus RTV 100 mg, both **twice daily with food**
- The use of COBI **is not recommended** with DRV 600 mg twice daily.

recommended doses for each weight band. It is important to provide careful instructions to caregivers when recommending a combination of different-strength tablets.

- Store DRV tablets and oral suspension at room temperature (25°C or 77°F). Suspension must be shaken well before dosing.
- **Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (FTC) or TAF. Severe acute exacerbation of HBV infection can occur when FTC or TAF are discontinued; therefore, liver function should be monitored for several months after patients with HBV infection stop taking FTC or TAF.**

**Metabolism/Elimination**

- Cytochrome P450 3A4 substrate and inhibitor.

**Darunavir Dosing in Patients with Hepatic Impairment:**

- DRV is primarily metabolized by the liver. Caution should be used when administering DRV to patients with hepatic impairment. DRV **is not recommended** in patients with severe hepatic impairment.

**Darunavir Dosing in Patients with Renal Impairment:**

- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30–60 mL/min).

### [Prezcobix] Darunavir/Cobicistat

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated with Darunavir Resistance:*

- One tablet once daily with food

### [Symtuza] Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet once daily with food in ARV-naive patients or in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) for at least 6 months with no known mutations associated with resistance to DRV or tenofovir.

- <sup>a</sup> Once-daily dosing of DRV is approved by the Food and Drug Administration (FDA), but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not generally recommend using this dosing schedule in children (see Frequency of Administration below).
- <sup>b</sup> Note that the dose in children weighing 10 kg to 15 kg is DRV 20 mg/kg plus RTV 3 mg/kg of body weight per dose, which is higher than the weight-adjusted dose in children with higher weights.
- <sup>c</sup> RTV 80 g/mL oral solution.
- <sup>d</sup> The volumes for the 375-mg and 450-mg DRV doses are rounded for suspension-dose convenience.
- <sup>e</sup> Some Panel members recommend using the FDA-approved dose of once-daily DRV 675 mg (administered using a combination of tablets) plus RTV 100 mg once daily for adolescents weighing  $\geq 30$  kg to  $< 40$  kg (see Table B below).
- <sup>f</sup> See the [Cobicistat](#) section for important information about toxicity, drug interactions, and monitoring in patients who receive COBI.

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

- **Metabolism:** Darunavir (DRV) is primarily metabolized by cytochrome P450 (CYP) 3A4. Both ritonavir (RTV) and cobicistat (COBI) are inhibitors of CYP3A4, thereby increasing the plasma concentration of DRV. Coadministration of DRV plus RTV (DRV/r) or DRV plus COBI (DRV/c) with drugs that are highly dependent on CYP3A clearance creates potential for multiple drug-drug interactions and may be associated with serious and/or life-threatening events or suboptimal efficacy.
- Coadministration of several drugs, including other protease inhibitors and rifampin, is **contraindicated** with DRV/r and DRV/c. A study involving adults with HIV suggested that etravirine (ETR) may reduce serum DRV concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent.<sup>1</sup> Before administering DRV **with a pharmacokinetic (PK) enhancer (boosting agent)**, a patient's medication profile should be carefully reviewed for potential drug interactions.
- When twice-daily DRV/r was used in combination with tenofovir disoproxil fumarate (TDF) in 13 patients with HIV aged 13 to 16 years, both TDF and DRVdarunavir exposures were lower than those found in adults treated with the same combination.<sup>2</sup> No dose adjustment is recommended when using DRV/r with TDF, but caution is advised and therapeutic drug monitoring (TDM) may be useful. Data from the IMPAACT protocol P1058A indicate that coadministering once-daily DRV/r with once-daily or twice-daily ETR in children, adolescents, and young adults aged 9 years to  $< 24$  years did not have a significant effect on DRV plasma concentrations.<sup>3</sup> When DRV/r was coadministered with ETR twice daily in pediatric patients, target concentrations for both DRV and ETR were achieved.<sup>4</sup> DRV PKs were

not affected when DRV was coadministered with rilpivirine (RPV) in a study of adolescents and young adults.<sup>5</sup> DRV/r coadministration increased RPV exposure two-fold to three-fold; close monitoring for RPV-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 (ARV) therapy in treatment-naïve and treatment-experienced children aged  $\geq 3$  years.

COBI (as Tybost) is approved by the FDA to be coadministered with DRV in pediatric patients weighing  $\geq 40$  kg. COBI is also approved by the FDA as a component of Symtuza (DRV/c/emtricitabine/tenofovir alafenamide) in pediatric patients weighing  $\geq 40$  kg. Although the FDA has not approved the use of COBI coformulated with DRV (as PrezcoBix), the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends the use of this fixed-dose combination (FDC) tablet in pediatric patients weighing  $\geq 40$  kg based on FDA approval of the component drugs.

#### *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.<sup>6,7</sup>

A randomized, open-label, multicenter pediatric trial that evaluated twice-daily DRV/r among 80 treatment-experienced children aged 6 years to  $< 18$  years reported that 66% of patients had plasma HIV RNA  $< 400$  copies/mL and 51% had HIV RNA  $< 50$  copies/mL at Week 24.<sup>7,8</sup>

Once-daily DRV/r has been investigated in a small study involving 12 treatment-experienced children aged 6 to 12 years who had maintained HIV viral loads  $< 50$  copies/mL for at least 6 months.<sup>9</sup> All but one child continued to have undetectable viral loads during a median of 11.6 months of follow-up (range 0.5-14.2 months). The remaining child had detectable viral load measurements between 20 copies/mL and 200 copies/mL on three occasions during a 3-month period before again becoming undetectable, without a change in regimen.

In one study, 12 participants aged 12 to 17 years received DRV/r once daily.<sup>10</sup> After 48 weeks, all but one participant had viral loads  $< 50$  copies/mL.

### **Pharmacokinetics and Dosing**

#### *Pharmacokinetics in Children Aged 3 Years to $< 6$ Years*

Twenty-one children aged 3 years to  $< 6$  years and weighing 10 kg to  $< 20$  kg received twice-daily DRV/r oral suspension. These children had experienced virologic failure on their previous ARV regimens and had fewer than three DRV resistance mutations, confirmed by genotypic testing.<sup>6-8</sup> The DRV area under the curve (AUC<sub>0-12h</sub>), 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.<sup>6-8</sup>

### Pharmacokinetics in Children Aged >6 Years

Initial pediatric PK evaluation of DRV tablets and RTV oral solution or tablets was based on a Phase 2 randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 years to <18 years and weighing  $\geq 20$  kg.<sup>11</sup> Part 1 of the trial used a weight-adjusted dose of DRV (9 mg/kg to 15 mg/kg) and RTV (1.5 mg/kg to 2.5 mg/kg) twice daily, **approximating** the standard adult dose of DRV/r 600 mg/100 mg twice daily **on a per-weight basis**. This dose resulted in inadequate drug exposure in the pediatric population studied, with a 24-hour AUC (AUC<sub>24h</sub>) that was 81% of the AUC<sub>24h</sub> observed in adults and a pre-dose concentration (C<sub>0h</sub>) that was 91% of the C<sub>0h</sub> observed in adults. A pediatric dose that was 20% to 33% higher than the directly scaled adult dose was needed to achieve a drug exposure that was similar to that found in adults, and this was the dose selected for Part 2 of the study. The higher dose used for the safety and efficacy evaluation was DRV 11 mg/kg to 19 mg/kg and RTV 1.5 mg/kg to 2.5 mg/kg twice daily. This dose resulted in a DRV AUC<sub>24h</sub> of 123.3 mcg·h/mL (range 71.9–201.5 mcg·h/mL) and a C<sub>0h</sub> of 3,693 ng/mL (range 1,842–7,191 ng/mL), representing 102% and 114% of the respective values in adults. Doses were given twice daily and were stratified into body-weight bands of 20 kg to <30 kg and 30 kg to <40 kg. The current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 kg to <40 kg were selected using the findings from the safety and efficacy portion of this study (see Table A).

A small study that involved 12 treatment-experienced children aged 6 to 12 years examined the PKs and efficacy of DRV/r once daily administered in combination with abacavir and lamivudine.<sup>9</sup> 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:<sup>12</sup> 600 mg/100 mg for patients weighing 15 kg to 30 kg, 675 mg/100 mg for patients weighing 30 kg to 40 kg, and 800 mg/100 mg for patients weighing >40 kg. The geometric mean AUC<sub>0-24h</sub> 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).<sup>13</sup> One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to DRV; the AUC<sub>0-24</sub> 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 <sub>12h</sub> (mcg·h/mL) Median <sup>a</sup>	C <sub>0h</sub> (ng/mL) Median <sup>a</sup>
Children Weighing 10 kg to <15 kg <sup>a</sup>	13	20 mg/kg/3 mg/kg	66.0	3,533
Children Weighing 10 kg to <15 kg <sup>a</sup>	4	25 mg/kg/3 mg/kg	116.0	8,522
Children Weighing 15 kg to <20 kg <sup>a</sup>	11	20 mg/kg/3 mg/kg	54.2	3,387
Children Weighing 15 kg to <20 kg <sup>a</sup>	14	25 mg/kg/3 mg/kg	68.6	4,365
Children Aged 6 Years to <12 Years <sup>b</sup>	24	Determined by weight bands <sup>b</sup>	56.4	3,354
Adolescents Aged 12 Years to <18 Years <sup>b</sup>	50	Determined by weight bands <sup>b</sup>	66.4	4,059
Adults Aged >18 Years (Three studies) <sup>c</sup>	285/278/119	600 mg/100 mg	54.7–61.7	3,197–3,539

<sup>a</sup> Source: Food and Drug Administration. FDA pharmacokinetics review. 2011. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf>.

<sup>b</sup> 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  $\geq 40$  kg. Data from the 2008 FDA pharmacokinetics review. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf>.

<sup>c</sup> Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021976s043.202895s0171bledt.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043.202895s0171bledt.pdf).

**Key:** AUC<sub>12h</sub> = 12-hour area under the curve; C<sub>0h</sub> = pre-dose concentration; DRV/r = darunavir/ritonavir; FDA = Food and Drug Administration

## Dosing

### Pharmacokinetic Enhancers

DRV should not be used without a PK enhancer (boosting agent). RTV may be used as a boosting agent in children and adults. **COBI may be used as a boosting agent in children weighing  $\geq 40$  kg and adults.**

A study that enrolled 19 Thai children used the RTV 100-mg capsule twice daily as the boosting dose for twice-daily DRV 375 mg (in children weighing 20 kg to  $< 30$  kg), 450 mg (in children weighing 30–40 kg), and 600 mg (in children weighing  $\geq 40$  kg).<sup>14</sup> The DRV exposures with RTV 100 mg twice daily were similar to those obtained in the studies with lower ( $< 100$  mg) doses of liquid RTV.<sup>11,14</sup> The tolerability and PK data from this small study support the use of RTV 100 mg for boosting, using either the powder or tablet formulation, in children weighing  $\geq 20$  kg, particularly in instances where the lower-dose formulations are unavailable or a child does not tolerate the liquid RTV formulation. There are no data available on the safety and tolerability of using the RTV 100-mg tablet or powder formulation in children weighing  $< 20$  kg.

Data on the dosing of DRV/c are available primarily for adult patients.<sup>15</sup> Data on once-daily use of the FDC tablet DRV/c 800 mg/150 mg (Prezcobix) showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.<sup>13</sup>

**In an open-label switch study, eight adolescent patients with a median age of 14 years (range 12–17 years) who received DRV/c had DRV exposures ( $AUC_{\tau}$ ) that were similar to those observed in adults, except for a lower trough concentration at the end of the dosing interval ( $C_{\tau}$ ). The median DRV  $C_{\tau}$  (494 ng/mL) was above the protein binding-adjusted half-maximal inhibitory concentration for wild-type virus (55 ng/mL). Adolescent patients in this study received the adult dose of COBI 150 mg daily. DRV dosing was based on weight, with patients who weighed  $\geq 40$  kg receiving DRV 800 mg once daily and patients who weighed 30 kg to  $< 40$  kg receiving DRV 675 mg once daily. In this small sample, 95.5% of patients had HIV RNA  $< 50$  copies/mL at Week 12. COBI appeared to be well tolerated with no discontinuations due to adverse events.<sup>16</sup>**

### Frequency of Administration

In February 2013, the FDA approved the use of once-daily DRV for treatment-naïve children and for treatment-experienced children without DRV 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.<sup>7,17</sup> Currently, there is limited data on the efficacy of once-daily DRV/r dosing in treatment-naïve or treatment-experienced children aged  $< 6$  years. Therefore, the Panel generally recommends dosing DRV/r twice daily in children aged  $\geq 3$  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-naïve and treatment-experienced adolescents weighing  $\geq 40$  kg who do not have mutations that are associated with DRV resistance. If DRV and RTV are used once daily in children aged  $< 12$  years, the Panel recommends conducting a PK evaluation of plasma concentrations of DRV and closely monitoring viral load.

**Table B. Food and Drug Administration-Approved Dosing for Pediatric Patients Aged  $\geq 3$  Years and Weighing  $>10$  kg who are Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations**

**Note:** The Panel generally recommends dosing DRV plus RTV twice daily in children aged  $\geq 3$  years to  $<12$  years.

Weight	Dose (Once Daily with Food)
10 kg to $<11$ kg <sup>a</sup>	DRV 350 mg (3.6 mL) <sup>b</sup> plus RTV 64 mg (0.8 mL) <sup>c</sup>
11 kg to $<12$ kg <sup>a</sup>	DRV 385 mg (4 mL) <sup>b</sup> plus RTV 64 mg (0.8 mL) <sup>c</sup>
12 kg to $<13$ kg <sup>a</sup>	DRV 420 mg (4.2 mL) plus RTV 80 mg (1 mL) <sup>c</sup>
13 kg to $<14$ kg <sup>a</sup>	DRV 455 mg (4.6 mL) <sup>b</sup> plus RTV 80 mg (1 mL) <sup>c</sup>
14 kg to $<15$ kg	DRV 490 mg (5 mL) <sup>b</sup> plus RTV 80 mg (1 mL) <sup>c</sup>
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) <sup>c</sup>
30 kg to $<40$ kg	DRV 675 mg (combination of tablets or 6.8 mL) <sup>b,d</sup> plus RTV 100 mg (tablet or 1.25 mL) <sup>c</sup>
$\geq 40$ kg	DRV 800 mg (tablet, combination of tablets, or 8 mL) <sup>d</sup> plus RTV 100 mg (tablet or 1.25 mL) <sup>c</sup>

<sup>a</sup> 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.

<sup>b</sup> RTV 80 mg/mL oral solution.

<sup>c</sup> The 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.

<sup>d</sup> The 6.8-mL and 8-mL DRV doses can be taken as two administrations (3.4 mL and 4 mL, respectively) once daily by refilling the oral dosing syringe supplied by the manufacturer, or as one administration once daily if a larger syringe is provided by a pharmacy or provider.

**Key:** DRV = darunavir; the Panel = the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; RTV = ritonavir

*Once-Daily Administration in Children Aged  $<12$  Years and Weighing  $<40$  kg*

During the TMC114-C228 trial, the researchers investigated once-daily dosing of DRV for 2 weeks; DRV PKs were evaluated in treatment-experienced children aged 3 years to  $<12$  years as part of a substudy. After the conclusion of the substudy, the participants switched back to a twice-daily regimen.<sup>17,18</sup> The DRV/r dose for once-daily use, which was based on PK simulation and which did not include a relative bioavailability factor, was DRV 40 mg/kg coadministered with approximately 7 mg/kg of RTV for children weighing  $<15$  kg, and DRV/r 600 mg/100 mg once daily for children weighing  $\geq 15$  kg.<sup>17,18</sup> The PK data obtained from 10 children aged 3 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 to 12 years,<sup>9</sup> the geometric mean AUC<sub>0-24h</sub> achieved was below the study target of 80% of the value seen in adults (63.1 mg·h/L vs. 71.8 mg·h/L). Trough values exceeded the plasma concentration that is recommended for treatment-experienced patients (0.55 mg/L). Despite the FDA dosing guidelines, the Panel generally recommends dosing DRV/r twice daily in children aged  $\geq 3$  years to  $<12$  years. The Panel makes this recommendation because of the small set of data used for once-daily DRV/r PK modeling and the limited amount of data on the use of once-daily DRV/r in children aged  $<12$  years.

**Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Background Therapy**

PK Parameter	Children Aged 3 Years to 6 Years (n = 10) <sup>18</sup>	Adults (n = 335)
DRV AUC <sub>24h</sub> geometric mean, ng·h/mL (SD)	115 (40.6)	89.7 (27.0)
DRV C <sub>0h</sub> geometric mean, ng/mL (SD)	3,029 (1,715)	2,027 (1,168)

**Key:** AUC<sub>24h</sub> = 24-hour area under the curve; C<sub>0h</sub> = pre-dose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

### Once-Daily Administration in Adolescents Aged $\geq 12$ and Weighing $\geq 40$ kg

A substudy of once-daily dosing of DRV/r 800 mg/100 mg demonstrated that DRV exposures in 12 treatment-naive adolescents (aged 12 to 17 years and weighing  $\geq 40$  kg) were similar to those seen in adults treated with once-daily DRV (see Table D).<sup>19</sup> After 48 weeks, 83.3% of patients had viral loads  $< 50$  copies/mL and 91.7% had viral loads  $< 400$  copies/mL.<sup>10</sup> Interestingly, no relationship was observed between DRV AUC<sub>24h</sub> and C<sub>0h</sub> and virologic outcome (HIV RNA  $< 50$  copies/mL) in this study. DRV exposures were found to be similar to those observed in adults with once-daily dosing in another study in which a single dose of DRV 800 mg with RTV 100 mg was administered to 24 subjects with a median age of 19.5 years (range 14–23 years).<sup>20</sup> However, DRV exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting that higher doses may be needed in younger adolescents. A single case report involving a highly treatment-experienced adolescent patient suggests that using an increased DRV dose with standard RTV boosting and employing TDM can lead to virologic suppression.

**Table D. Darunavir Pharmacokinetics with Once-Daily Administration in Adolescents Aged  $\geq 12$  Years and Adults Aged  $> 18$  Years**

Population	N	Dose of DRV/r	AUC <sub>24h</sub> <sup>a</sup> (mcg*h/mL) Median	C <sub>0h</sub> (ng/mL) Median
Adolescents Aged 12 to 17 Years (mean age 14.6 years) <sup>19</sup>	12	800 mg/100 mg	86.7	2,141
Adolescents and Adults Aged 14 to 23 Years (mean age 19.5 years) <sup>20</sup>	24	800 mg/100 mg	69.5	1,300
Adults Aged $> 18$ Years (Two studies) <sup>a</sup>	335/280	800 mg/100 mg	87.8–87.9	1,896–2,041

<sup>a</sup> Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021976s043.202895s0171bledt.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043.202895s0171bledt.pdf)

**Key:** AUC<sub>24h</sub> = 24-hour area under the curve; C<sub>0h</sub> = pre-dose concentration; DRV/r = darunavir/ritonavir

The efficacy of once-daily DRV has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.<sup>10,21</sup>

## References

1. Belkhir L, Elens L, Zech F, et al. Interaction between darunavir and etravirine is partly mediated by CYP3A5 polymorphism. *PLoS One*. 2016;11(10):e0165631. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27788239>.
2. King JR, Yogev R, Jean-Philippe P, et al. Steady-state pharmacokinetics of tenofovir-based regimens in HIV-infected pediatric patients. *Antimicrob Agents Chemother*. 2011;55(9):4290-4294. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21670182>.
3. Larson KB, Cressey TR, Yogev R, et al. Pharmacokinetics of once-daily darunavir/ritonavir with and without etravirine in human immunodeficiency virus-infected children, adolescents, and young adults. *J Pediatric Infect Dis Soc*. 2016;5(2):131-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27199469>.
4. Cressey TR, Yogev R, Wiznia A, et al. Pharmacokinetics of darunavir/ritonavir with etravirine both twice daily in human immunodeficiency virus-infected adolescents and young adults. *J Pediatric Infect Dis Soc*. 2017;6(3):294-296. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27103489>.
5. Foca M, Yogev R, Wiznia A, et al. Rilpivirine pharmacokinetics without and with darunavir/ritonavir once daily in adolescents and young adults. *Pediatr Infect Dis J*. 2016;35(9):e271-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27187753>.
6. Violari A, Bologna R, Kumarasamy N, et al. Safety and efficacy of darunavir/ritonavir in treatment-experienced pediatric patients: week 48 results of the ARIEL trial. *Pediatr Infect Dis J*. 2015;34(5):e132-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25719453>.

7. Darunavir [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/021976s054,202895s0251bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021976s054,202895s0251bl.pdf).
8. Food and Drug Administration. Clinical review of darunavir. 2011. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf>.
9. Bastiaans DET, Geelen SPM, Visser EG, et al. Pharmacokinetics, short-term safety and efficacy of the approved once-daily darunavir/ritonavir dosing regimen in HIV-infected children. *Pediatr Infect Dis J*. 2018;37(10):1008-1010. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29474261>.
10. Flynn P, Komar S, Blanche S, et al. Efficacy and safety of darunavir/ritonavir at 48 weeks in treatment-naïve, HIV-1-infected adolescents: results from a Phase 2 open-label trial (DIONE). *Pediatr Infect Dis J*. 2014;33(9):940-945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25361024>.
11. Blanche S, Bologna R, Cahn P, et al. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents. *AIDS*. 2009;23(15):2005-2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19724191>.
12. Brochot A, Kakuda TN, Van De Castele T, et al. Model-based once-daily darunavir/ritonavir dosing recommendations in pediatric HIV-1-infected patients aged  $\geq 3$  to  $< 12$  years. *CPT Pharmacometrics Syst Pharmacol*. 2015;4(7):406-414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26312164>.
13. Kakuda TN, Brochot A, Tomaka FL, Vangeneugden T, Van De Castele T, Hoetelmans RM. Pharmacokinetics and pharmacodynamics of boosted once-daily darunavir. *J Antimicrob Chemother*. 2014;69(10):2591-2605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24951533>.
14. Chokephaibulkit K, Prasitsuebsai W, Wittawatmongkol O, et al. Pharmacokinetics of darunavir/ritonavir in Asian HIV-1-infected children aged  $\geq 7$  years. *Antivir Ther*. 2012;17(7):1263-1269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22954687>.
15. Tybost (Cobicistat) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/203094s0141bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203094s0141bl.pdf).
16. McFarland E, Heresi G, Batra J, et al. Pharmacokinetics, safety, and efficacy of atv or drv with cobi in adolescents. Abstract 425. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/pharmacokinetics-safety-and-efficacy-atv-or-drv-cobi-adolescents>.
17. Prezista drug Label. Clinical review of darunavir. [package insert]. Food and Drug Administration. 2012. Available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM346671.pdf>.
18. Kakuda TN, Brochot A, van de Castele T, Opsomer M, Tomaka F. Establishing darunavir dosing recommendations in treatment-naïve and treatment-experienced pediatric patients. Presented at: Clinical Pharmacology Workshop on HIV. 2013. Amsterdam, Netherlands. Available at: [http://www.natap.org/2013/Pharm/Pharm\\_19.htm](http://www.natap.org/2013/Pharm/Pharm_19.htm).
19. Flynn P, Blanche S, Giaquinto C, et al. . 24-week efficacy, safety, tolerability and pharmacokinetics of darunavir/ritonavir once daily in treatment-naïve adolescents aged 12 to  $< 18$  years in DIONE. Abstract # PP\_2. Presented at: International Workshop on HIV Pediatrics. 2011. Rome, Italy. Available at: [http://www.natap.org/2011/IAS/IAS\\_40.htm](http://www.natap.org/2011/IAS/IAS_40.htm).
20. King J, Hazra R, et al. Pharmacokinetics of darunavir 800 mg with ritonavir 100mg once daily in HIV+ adolescents and young adults. Presented at: Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, GA.
21. Chokephaibulkit K, Rungmaitree S, Phongsamart W, et al. Pharmacokinetics and efficacy of darunavir/ritonavir once daily in virologically suppressed, treatment-experienced HIV-infected children. *HIV Med*. 2014;15(8):511-512. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25138061>.

## Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 14, 2020; last reviewed April 14, 2020)

### 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

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Neonate (Aged <14 Days) Dose:

- Lopinavir/ritonavir (LPV/r) is not approved by the Food and Drug Administration (FDA) for use in neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, when no alternatives are available for neonates who have not met these age thresholds, some members of the Panel would consider using LPV/r oral solution at a dose of 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily in combination with careful monitoring of serum osmolality, serum creatinine, liver function enzymes, cardiac function, and electrolytes. This use of LPV/r is based on limited research and clinical experience. The potential benefit of using LPV/r in premature infants must be carefully balanced with the risk of metabolic and cardiac toxicity.

#### 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<sup>2</sup> of body surface area per dose twice daily. This approximates LPV/r 16 mg/4 mg (both per kg body weight) twice daily. Use of this dose in infants aged <12 months is associated with lower LPV trough levels than those found in adults; LPV dosing should be adjusted for growth at frequent intervals (see text below). Also see text for information on transitioning infants to the lower mg per m<sup>2</sup> 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 Formulations).
- LPV/r oral solution can be kept at room temperature (up to 77°F or 25°C) if used within 2 months. If kept refrigerated (36°F to 46°F or 2°C to 8°C), LPV/r oral solution remains stable until the expiration date printed on the label.
- Children aged <18 years who receive once-daily dosing of LPV/r have shown

*Child and Adolescent (Aged >12 Months to 18 Years) Dose:*

- Once-daily dosing **is not recommended**.
- LPV/r 300 mg/75 mg per m<sup>2</sup> 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 approximates LPV/r 11 mg/2.75 mg (both per kg body weight) twice daily. This dose is routinely used by many clinicians and is the preferred dose for antiretroviral therapy (ART)-experienced patients who could harbor virus with decreased LPV susceptibility (see text below).
- LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients weighing <15 kg, this dose approximates LPV/r 12 mg/3 mg per kg body weight given twice daily. For patients weighing ≥15 kg to 40 kg, this dose approximates LPV/r 10 mg/2.5 mg per kg body weight given twice daily. This lower dose **should not be used** in treatment-experienced patients who could harbor virus with decreased LPV susceptibility.

**Weight-Band Dosing for Lopinavir 100 mg/Ritonavir 25 mg Pediatric Tablets in Children and Adolescents**

	Recommended Number of LPV/r 100 mg/25 mg Tablets Given Twice Daily	
<b>Dosing Target</b>	300 mg/m <sup>2</sup> per dose given twice daily	230 mg/m <sup>2</sup> per dose given twice daily
<b>Body Weight</b>		
<b>15 kg to 20 kg</b>	2	2
<b>&gt;20 kg to 25 kg</b>	3	2
<b>&gt;25 kg to 30 kg</b>	3	3
<b>&gt;30 kg to 35 kg</b>	4 <sup>a</sup>	3
<b>&gt;35 kg to 45 kg</b>	4 <sup>a</sup>	4 <sup>a</sup>
<b>&gt;45 kg</b>	4 <sup>a</sup> or 5 <sup>b</sup>	4 <sup>a</sup>

<sup>a</sup> 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.

<sup>b</sup> In patients who weigh >45 kg and who are receiving concomitant nevirapine (NVP), efavirenz (EFV), fosamprenavir (FPV), or nelfinavir (NFV), the FDA-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

considerable variability in plasma concentrations and have a higher incidence of diarrhea. Therefore, once-daily dosing **is not recommended** for this age group.

- Use of LPV/r once daily is **contraindicated** if three or more of the following LPV resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher LPV trough concentrations may be required to suppress resistant virus.

**Metabolism/Elimination**

- Cytochrome P450 3A4 substrate and inhibitor.

**Lopinavir/Ritonavir Dosing in Patients with Hepatic Impairment:**

- LPV/r is primarily metabolized by the liver. Use caution when administering LPV to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the coformulation of LPV/r, ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of LPV and increasing LPV plasma concentrations.

*Adult (Aged >18 Years) Dose:*

- LPV/r 800 mg/200 mg once daily; *or*
- LPV/r 400 mg/100 mg twice daily
- **Do not use** once-daily dosing in children; adolescents; in patients receiving concomitant therapy with NVP, EFV, FPV, or NFV; or in patients with three or more LPV-associated mutations (see Special Instructions for a list of mutations).

**Dosing for Individuals with Three or More Lopinavir-Associated Mutations (See Special Instructions for List):**

- LPV/r 400 mg/100 mg twice daily

**Dosing for Individuals Receiving Concomitant Nevirapine or Efavirenz:**

- These drugs induce LPV metabolism and reduce LPV plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs. Once-daily dosing **should not be used** in these patients.

*Child and Adolescent (Aged >12 Months to 18 Years) Dose:*

- LPV/r 300 mg/75 mg per m<sup>2</sup> 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**.

**Lopinavir/Ritonavir 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 (CYP) 3A4 substrate and inhibitor with the potential for multiple drug interactions. Coadministering LPV/r with drugs that induce CYP3A4 may decrease LPV plasma concentrations, while coadministering LPV/r with other CYP3A4 inhibitors may increase LPV plasma concentrations. Coadministering LPV/r with other CYP3A4 substrates may require dose adjustments and additional monitoring.
- Before initiating therapy with LPV/r, a patient's medication profile should be carefully reviewed for potential drug interactions. In patients treated with LPV/r, fluticasone (a commonly used inhaled and

intranasal steroid) should be avoided, and an alternative steroid should be used. Drug interactions with antituberculous drugs are common; patients who are receiving both LPV/r and antituberculous drugs may need a dose adjustment for LPV/r, or they may need to switch to an antiretroviral (ARV) regimen that does not include LPV/r.

### Major Toxicities

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, insulin resistance.<sup>1</sup> Hyperlipidemia, especially **hypercholesterolemia** and hypertriglyceridemia,<sup>2-4</sup> which may be more pronounced in girls than in boys.<sup>5</sup> LPV requires a higher dose of ritonavir (RTV) than some other protease inhibitors (PIs); this higher dose may exacerbate these adverse events (AEs).
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, hemolytic anemia, spontaneous and/or increased bleeding in hemophiliacs, pancreatitis, elevation in serum transaminases, hepatitis (which has been life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and Torsades de Pointes may occur.
- *Special populations—neonates:* An increased risk of toxicity in premature infants has been reported, including cases of transient symptomatic adrenal insufficiency,<sup>6,7</sup> life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),<sup>8-10</sup> lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be caused by the drug itself and/or from the inactive ingredients in the oral solution, which include propylene glycol 15.3% and ethanol 42.4%.<sup>10</sup> Transient asymptomatic elevation in 17-hydroxyprogesterone levels has also been reported in term newborns treated at birth with LPV/r.<sup>6</sup> 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. **A total of 25 neonates with HIV were enrolled, with a median birth weight of 2,130 g (interquartile range [IQR] 1,775–2,630 g) and a median gestational age of 35 weeks (IQR 32–37 weeks).** Neonates received LPV/r solution at a dose of 300 mg/75 mg per m<sup>2</sup> twice daily, which was well tolerated and not associated with any treatment-related AEs, even in 13 newborns who initiated therapy prior to 42 weeks postmenstrual age at a mean postnatal age of 37 days (range 13–61 days).<sup>11</sup>

### 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 neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. **However, when no alternatives are available for neonates who have not met these age thresholds, some members of the Panel would consider using LPV/r oral solution at a dose of 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily in combination with careful monitoring of serum osmolality, serum creatinine, liver function enzymes, cardiac function, and electrolytes. This use of LPV/r is based on limited research and clinical experience. The potential benefit of using LPV/r in premature infants must be carefully balanced with the risk of metabolic and cardiac toxicity. In pediatric patients receiving LPV/r at a dose of 300 mg/75 mg per m<sup>2</sup> twice daily, lower LPV exposure has been observed in infants aged <6 weeks relative to older children.**<sup>12</sup>

#### Efficacy

Clinical trials involving ART-naïve adults have shown that regimens that contain LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens, including regimens that contain atazanavir, darunavir (DRV), fosamprenavir (FPV), saquinavir/ritonavir, or efavirenz (EFV). Studies have also shown that regimens that contain LPV/r plus two NRTIs are superior to regimens that

contain nelfinavir (NFV) and inferior to regimens that contain DRV.<sup>13-21</sup>

LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and acceptable toxicity.<sup>22-30</sup>

### Pharmacokinetics

#### General Considerations

Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 m<sup>2</sup>. For the adult dose of LPV/r 400 mg/100 mg, the scaled pediatric dose would be approximately LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area. However, younger children have enhanced LPV clearance and need higher doses to achieve LPV exposures that are similar to those seen in adults treated with standard doses. To achieve a C<sub>trough</sub> 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. LPV exposures in infants<sup>12,24,29</sup> are compared to those in older children<sup>22</sup> and adults<sup>31</sup> in Table A below.

**Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age**

PK Parameters	Adults (n = 19) <sup>31</sup>	Children (n = 12) <sup>22</sup>	Children (n = 15) <sup>22</sup>	Infants <sup>a</sup> at 12 Months (n = 20) <sup>29</sup>	Infants at 6 Weeks–6 Months (n = 18) <sup>24</sup>	Infants at 14 Days to <6 Weeks (n = 9) <sup>12</sup>
LPV Dose	400 mg	230 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>	300 mg/m <sup>2</sup>
AUC <sub>0-12</sub> (mcg·hr/mL)	92.6	72.6	116.0	101.0	74.5	43.4
C <sub>max</sub> (mcg/mL)	9.8	8.2	12.5	12.1	9.4	5.2
C <sub>trough</sub> (mcg/mL)	7.1	4.7	7.9	4.9	2.7	2.5
C <sub>min</sub> (mcg/mL)	5.5	3.4	6.5	3.8	2.0	1.4

<sup>a</sup> This column contains unreported data that were originally generated for a published study. The data were provided by Edmund Capparelli, PharmD in a personal communication (April 18, 2012).

**Note:** Values are means; all data comes from studies where none of the participants received NNRTIs as part of their ART.

**Key:** ART = antiretroviral therapy; AUC = area under the curve; LPV = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitors; PK = pharmacokinetic

Models suggest that diet, body weight, and postnatal age are important factors in LPV PKs, with improved bioavailability as dietary fat increases during the first year of life<sup>32</sup> and with clearance slowing by age 2.3 years.<sup>33</sup> A study from the United Kingdom and Ireland compared outcomes of LPV/r treatment with either 230 mg per m<sup>2</sup> of body surface area per dose or 300 mg per m<sup>2</sup> of body surface area per dose in children aged 5.6 to 12.8 years at the time of LPV/r initiation. The findings suggested that the higher dose was associated with improved long-term viral load suppression.<sup>34</sup>

### Pharmacokinetics and Dosing

#### 14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

The PKs of the oral solution at approximately LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily was evaluated in infants aged <6 weeks<sup>12</sup> and infants aged 6 weeks to 6 months.<sup>24</sup> Even at this higher dose, C<sub>trough</sub> levels were highly variable, but they were lower in infants than in children aged >6 months. C<sub>trough</sub> levels were lower in infants aged ≤6 weeks than in infants aged 6 weeks to 6 months. By age 12 months, LPV area under the curve (AUC) was similar to that found in older children.<sup>29</sup> Because infants grow rapidly in the first months of life, it is important to optimize LPV dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg per m<sup>2</sup> of body surface area in older children and adolescents,<sup>25</sup> some practitioners anticipate rapid infant growth and prescribe doses somewhat higher

than the 300 mg per m<sup>2</sup> of body surface area dose to allow for projected growth between clinic appointments.

#### *12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

Lower trough concentrations have been observed in children receiving LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily than in children receiving LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (see Table A above).<sup>21</sup> Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (when LPV/r is given without nevirapine [NVP], EFV, FPV, or NFV), rather than the FDA-approved dose of LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily.

For infants receiving LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily, immediate dose reduction at age 12 months **is not recommended**; many practitioners would allow patients to “grow into” the LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily dose as they gain weight over time. Some practitioners would continue the infant dose (LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily) while using the LPV/r liquid formulation.

#### *Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir*

In both children and adults, the LPV C<sub>trough</sub> is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant FPV or NFV. Higher doses of LPV are recommended when the drug is given in combination with NVP, EFV, FPV, or NFV. In 14 children who were treated with LPV/r 230 mg/57.5 mg per m<sup>2</sup> of body surface area per dose twice daily plus NVP, the mean LPV C<sub>trough</sub> was 3.77 ± 3.57 mcg/mL.<sup>22</sup> Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, the variability in concentration is much higher in children than in adults.<sup>22,35</sup> In a study of 15 children with HIV aged 5.7 to 16.3 years who were treated with LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily plus EFV 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in LPV trough concentrations. Five of 15 children (33%) had LPV 12-hour trough concentrations that were <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.<sup>36</sup> A PK study in 20 children aged 10 to 16 years who were treated with LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area twice daily plus EFV 350 mg per m<sup>2</sup> of body surface area once daily reported only one patient (6.6%) with subtherapeutic LPV trough concentrations,<sup>37</sup> perhaps because the trial used an EFV dose that was approximately 11 mg/kg body weight<sup>37</sup> instead of the 14 mg/kg body weight dose used in the trial discussed above.<sup>36</sup>

### **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.<sup>38</sup> 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.<sup>39-42</sup> The currently available tablet formulation of LPV/r has lower variability in trough levels than the previously used soft-gel formulation.<sup>42,43</sup> 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 received once-daily doses had viral loads ≥50 copies/mL within 48 weeks.<sup>44</sup>

#### *Dosing and Its Relation to Efficacy*

LPV/r is effective in treatment-experienced patients with severe immune suppression,<sup>45,46</sup> although heavily pre-treated patients may be slower to reach undetectable viral loads<sup>46,47</sup> and may have less-robust CD4 T lymphocyte (CD4) percentage responses.<sup>48</sup>

The relationship between LPV exposure and the susceptibility of the HIV-1 isolate (EC<sub>50</sub>) is a key component of successful treatment. The ratio of C<sub>trough</sub> to EC<sub>50</sub> 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  $C_{\text{trough}}$  or  $EC_{50}$  alone.<sup>49-51</sup> One study investigated the use of the IQ as a guide for therapy by administering higher doses of LPV/r to children and adolescents until a target IQ of 15 was reached. This study showed that doses of LPV/r 400 mg/100 mg per  $m^2$  of body surface area per dose twice daily (without FPV, NFV, NVP, or EFV) and LPV/r 480 mg/120 mg per  $m^2$  of body surface area per dose twice daily (with NVP or EFV) were safe and tolerable.<sup>25</sup> Results of a modeling study suggest that standard doses of LPV/r may be inadequate for treatment-experienced children and suggest the potential utility of TDM when LPV/r is used in children who were previously treated with PIs.<sup>52</sup> An LPV plasma concentration of  $\geq 1$  mcg/mL is cited as a minimum target trough concentration,<sup>53-55</sup> but this concentration may not adequately control viremia in patients with multiple LPV resistance mutations.<sup>56,57</sup>

## Formulations

### Palatability

The poor palatability of the LPV/r oral solution can be a significant challenge to medication adherence for some children and families. Numbing the taste buds with ice chips before or after administering the solution, masking the taste of the solution by administering it with sweet or tangy foods (e.g., chocolate syrup, peanut butter), or having the pharmacist flavor the solution prior to dispensing it are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.<sup>58,59</sup>

### 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,  $C_{\text{max}}$ , and  $C_{\text{trough}}$  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.<sup>60</sup> In a PK study that used a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate LPV  $C_{\text{trough}}$  measurements.<sup>43</sup>

### 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.<sup>27,61-65</sup> However, one study did not observe this difference in the effect of LPV/r on CD4 count,<sup>66</sup> and another study found that the difference did not persist after a year of therapy.<sup>30</sup> Some studies found no differences between the weight gain of children treated with LPV/r and those treated with EFV.<sup>64,67</sup> Switching to an EFV-based regimen at or after age 3 years removed the risk of LPV-associated metabolic toxicity, with no loss of virologic control (see Table 16 in [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#)).<sup>64,65</sup> Bone mineral density improved when children were treated with EFV-containing regimens instead of regimens that contained LPV/r.<sup>68</sup>

## References

1. Dejkharnon P, Unachak K, Aurpibul L, Sirisanthana V. Insulin resistance and lipid profiles in HIV-infected Thai children receiving lopinavir/ritonavir-based highly active antiretroviral therapy. *J Pediatr Endocrinol Metab*. 2014;27(5-6):403-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24259240>.
2. Arpadi S, Shiao S, Strehlau R, et al. Metabolic abnormalities and body composition of HIV-infected children on lopinavir or nevirapine-based antiretroviral therapy. *Arch Dis Child*. 2013;98(4):258-264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23220209>.
3. Ige OO, Yilgwan CS, Ebonyi AO, et al. Serum lipid and glucose profiles in HIV-positive Nigerian children. *J Virus Erad*. 2017;3(3):157-162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28758024>.
4. Patel K, Lindsey J, Angelidou K, Aldrovandi G, Palumbo P, Team IPS. Metabolic effects of initiating lopinavir/

ritonavir-based regimens among young children. *AIDS*. 2018;32(16):2327-2336. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30102656>.

5. Shiao S, Kuhn L, Strehlau R, et al. Sex differences in responses to antiretroviral treatment in South African HIV-infected children on ritonavir-boosted lopinavir- and nevirapine-based treatment. *BMC Pediatr*. 2014;14:39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24521425>.
6. Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. *JAMA*. 2011;306(1):70-78. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21730243>.
7. Kariyawasam D, Peries M, Foissac F, et al. Lopinavir-ritonavir impairs adrenal function in infants. *Clin Infect Dis*. 2019;pii: ciz888 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31633158>.
8. Lopriore E, Rozendaal L, Gelinck LB, Bokenkamp R, Boelen CC, Walther FJ. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS*. 2007;21(18):2564-2565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025905>.
9. McArthur MA, Kalu SU, Foulks AR, Aly AM, Jain SK, Patel JA. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J*. 2009;28(12):1127-1129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19820426>.
10. Food and Drug Administration. Serious health problems seen in premature babies given kaletra (lopinavir/ritonavir) oral solution. 2011. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm246002.htm>.
11. Bekker A, Hanan N, Cababasy M, et al. Pharmacokinetics and safety of lopinavir/ritonavir solution in HIV-infected newborns. Abstract 841. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/pharmacokinetics-and-safety-lopinavirritonavir-solution-hiv-infected-newborns>.
12. Chadwick EG, Pinto J, Yogev R, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr Infect Dis J*. 2009;28(3):215-219. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19209098>.
13. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002;346(26):2039-2046. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12087139>.
14. Eron J, Jr., Yeni P, Gathe J, Jr., et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet*. 2006;368(9534):476-482. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16890834>.
15. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet*. 2008;372(9639):646-655. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18722869>.
16. Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS*. 2008;22(12):1389-1397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18614861>.
17. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008;358(20):2095-2106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18480202>.
18. Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. *HIV Clin Trials*. 2009;10(2):76-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19487177>.
19. Walmsley S, Baumgarten A, Berenguer J, et al. Dolutegravir plus abacavir/lamivudine for the treatment of HIV-1 infection in antiretroviral therapy-naïve patients: week 96 and week 144 results from the SINGLE randomized clinical trial. *J Acquir Immune Defic Syndr*. 2015;70(5):515-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26262777>.
20. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared

with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med.* 2013;14(1):49-59. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23088336>.

21. Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr.* 2010;53(3):323-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20032785>.
22. Saez-Llorens X, Violarì A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J.* 2003;22(3):216-224. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12634581>.
23. De Luca M, Miccinesi G, Chiappini E, Zappa M, Galli L, De Martino M. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol.* 2005;18(4):729-735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16388722>.
24. Chadwick EG, Capparelli EV, Yogev R, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008;22(2):249-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18097227>.
25. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother.* 2008;52(9):3276-3283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18625762>.
26. Violarì A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med.* 2008;359(21):2233-2244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19020325>.
27. Palumbo P, Lindsey JC, Hughes MD, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N Engl J Med.* 2010;363(16):1510-1520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20942667>.
28. Reitz C, Coovadia A, Ko S, et al. Initial response to protease-inhibitor-based antiretroviral therapy among children less than 2 years of age in South Africa: effect of cotreatment for tuberculosis. *J Infect Dis.* 2010;201(8):1121-1131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20214476>.
29. Chadwick EG, Yogev R, Alvero CG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *AIDS.* 2011;25(5):643-649. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21297419>.
30. Barlow-Mosha L, Angelidou K, Lindsey J, et al. Nevirapine- versus lopinavir/ritonavir-based antiretroviral therapy in HIV-infected infants and young children: long-term follow-up of the IMPAACT P1060 randomized trial. *Clin Infect Dis.* 2016;63(8):1113-1121. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27439527>.
31. Lopinavir/ritonavir (Kaletra) [package insert]. Food and Drug Administration. 2015. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/021226s0421bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021226s0421bl.pdf).
32. Nikanjam M, Chadwick EG, Robbins B, et al. Assessment of lopinavir pharmacokinetics with respect to developmental changes in infants and the impact on weight band-based dosing. *Clin Pharmacol Ther.* 2012;91(2):243-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22190064>.
33. Urien S, Firtion G, Anderson ST, et al. Lopinavir/ritonavir population pharmacokinetics in neonates and infants. *Br J Clin Pharmacol.* 2011;71(6):956-960. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21564164>.
34. Donegan K, Doerholt K, Judd A, et al. Lopinavir dosing in HIV-infected children in the United Kingdom and Ireland. *Pediatr Infect Dis J.* 2013;32(1):45-50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23076384>.
35. Verweel G, Burger DM, Sheehan NL, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. *Antivir Ther.* 2007;12(4):453-458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17668553>.
36. Bergshoeff AS, Fraaij PL, Ndagijimana J, et al. Increased dose of lopinavir/ritonavir compensates for efavirenz-induced drug-drug interaction in HIV-1-infected children. *J Acquir Immune Defic Syndr.* 2005;39(1):63-68. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15444444>.

[www.ncbi.nlm.nih.gov/pubmed/15851915](http://www.ncbi.nlm.nih.gov/pubmed/15851915).

37. King JR, Acosta EP, Yogev R, et al. Steady-state pharmacokinetics of lopinavir/ritonavir in combination with efavirenz in human immunodeficiency virus-infected pediatric patients. *Pediatr Infect Dis J*. 2009;28(2):159-161. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19106779>.
38. Gondrie IPE, Bastiaans DET, Fraaij PLA, et al. Sustained viral suppression in HIV-infected children on once-daily lopinavir/ritonavir in clinical practice. *Pediatr Infect Dis J*. 2017;36(10):976-980. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28475554>.
39. Rosso R, Di Biagio A, Dentone C, et al. Lopinavir/ritonavir exposure in treatment-naive HIV-infected children following twice or once daily administration. *J Antimicrob Chemother*. 2006;57(6):1168-1171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16606636>.
40. van der Lee M, Verweel G, de Groot R, Burger D. Pharmacokinetics of a once-daily regimen of lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther*. 2006;11(4):439-445. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16856617>.
41. la Porte C, van Heeswijk R, Mitchell CD, Zhang G, Parker J, Rongkavilit C. Pharmacokinetics and tolerability of once-versus twice-daily lopinavir/ritonavir treatment in HIV-1-infected children. *Antivir Ther*. 2009;14(4):603-606. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19578247>.
42. van der Flier M, Verweel G, van der Knaap LC, et al. Pharmacokinetics of lopinavir in HIV type-1-infected children taking the new tablet formulation once daily. *Antivir Ther*. 2008;13(8):1087-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19195335>.
43. Puthanakit T, Choikephaibulkit K, Suntarattiwong P, et al. Therapeutic drug monitoring of lopinavir in human immunodeficiency virus-infected children receiving adult tablets. *Pediatr Infect Dis J*. 2010;29(1):79-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19858772>.
44. Paediatric European Network for Treatment of AIDS. Once vs. twice-daily lopinavir/ritonavir in HIV-1-infected children. *AIDS*. 2015;29(18):2447-2457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26558544>.
45. Resino S, Bellon JM, Ramos JT, et al. Salvage lopinavir-ritonavir therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2004;23(10):923-930. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15602192>.
46. Resino S, Bellon JM, Munoz-Fernandez MA, Spanish Group of HIV Infection. Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency. *J Antimicrob Chemother*. 2006;57(3):579-582. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16446377>.
47. Resino S, Galan I, Perez A, et al. Immunological changes after highly active antiretroviral therapy with lopinavir-ritonavir in heavily pretreated HIV-infected children. *AIDS Res Hum Retroviruses*. 2005;21(5):398-406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15929702>.
48. Larru B, Resino S, Bellon JM, et al. Long-term response to highly active antiretroviral therapy with lopinavir/ritonavir in pre-treated vertically HIV-infected children. *J Antimicrob Chemother*. 2008;61(1):183-190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025025>.
49. Casado JL, Moreno A, Sabido R, et al. Individualizing salvage regimens: the inhibitory quotient ( $C_{trough}/IC_{50}$ ) as predictor of virological response. *AIDS*. 2003;17(2):262-264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12545089>.
50. Delaugerre C, Teglas JP, Treluyer JM, et al. Predictive factors of virologic success in HIV-1-infected children treated with lopinavir/ritonavir. *J Acquir Immune Defic Syndr*. 2004;37(2):1269-1275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15385734>.
51. Hsu A, Isaacson J, Brun S, et al. Pharmacokinetic-pharmacodynamic analysis of lopinavir-ritonavir in combination with efavirenz and two nucleoside reverse transcriptase inhibitors in extensively pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2003;47(1):350-359. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12499212>.
52. Rakhmanina N, van den Anker J, Baghdassarian A, Soldin S, Williams K, Neely MN. Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob Agents Chemother*. 2009;53(6):2532-2538. Available at: <http://www.ncbi.nlm.nih.gov/>

[pubmed/19258274](https://pubmed/19258274).

53. Moholisa RR, Schomaker M, Kuhn L, et al. Plasma lopinavir concentrations predict virological failure in a cohort of South African children initiating a protease-inhibitor-based regimen. *Antivir Ther*. 2014;19(4):399-406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24518130>.
54. Moholisa RR, Schomaker M, Kuhn L, et al. Effect of lopinavir and nevirapine concentrations on viral outcomes in protease inhibitor-experienced HIV-infected children. *Pediatr Infect Dis J*. 2016;35(12):e378-e383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27583591>.
55. Aurrpibul L, Teerananchai S, Prasitsuebsai W, et al. Therapeutic drug monitoring of lopinavir in HIV-infected children on second-line antiretroviral therapy in Asia. *Ther Drug Monit*. 2016;38(6):791-795. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27749514>.
56. van Zyl GU, van Mens TE, McIlleron H, et al. Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a resource-limited setting. *J Acquir Immune Defic Syndr*. 2011;56(4):333-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21239995>.
57. Court R, Gordon M, Cohen K, et al. Random lopinavir concentrations predict resistance on lopinavir-based antiretroviral therapy. *Int J Antimicrob Agents*. 2016;48(2):158-162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27345268>.
58. Food and Drug Administration. NDA 205425 tentative approval 2015. 2015. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/2015/205425Orig1s000TA1tr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/205425Orig1s000TA1tr.pdf).
59. Kekitiinwa A, Musiime V, Thomason MJ, et al. Acceptability of lopinavir/r pellets (minitabs), tablets and syrups in HIV-infected children. *Antivir Ther*. 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27128199>.
60. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Defic Syndr*. 2011;58(4):385-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21876444>.
61. Coovadia A, Abrams EJ, Stehlau R, et al. Reuse of nevirapine in exposed HIV-infected children after protease inhibitor-based viral suppression: a randomized controlled trial. *JAMA*. 2010;304(10):1082-1090. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823434>.
62. Violari A, Lindsey JC, Hughes MD, et al. Nevirapine versus ritonavir-boosted lopinavir for HIV-infected children. *N Engl J Med*. 2012;366(25):2380-2389. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22716976>.
63. Lindsey JC, Hughes MD, Violari A, et al. Predictors of virologic and clinical response to nevirapine versus lopinavir/ritonavir-based antiretroviral therapy in young children with and without prior nevirapine exposure for the prevention of mother-to-child HIV transmission. *Pediatr Infect Dis J*. 2014;33(8):846-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25222305>.
64. Murnane PM, Strehlau R, Shiao S, et al. Switching to efavirenz versus remaining on ritonavir-boosted lopinavir in HIV-infected children exposed to nevirapine: long-term outcomes of a randomized trial. *Clin Infect Dis*. 2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28419200>.
65. Coovadia A, Abrams EJ, Strehlau R, et al. Efavirenz-based antiretroviral therapy among nevirapine-exposed HIV-infected children in South Africa: a randomized clinical trial. *JAMA*. 2015;314(17):1808-1817. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26529159>.
66. Dahourou DL, Amorissani-Folquet M, Malateste K, et al. Efavirenz-based simplification after successful early lopinavir-boosted-ritonavir-based therapy in HIV-infected children in Burkina Faso and Cote d'Ivoire: the MONOD ANRS 12206 non-inferiority randomised trial. *BMC Med*. 2017;15(1):85. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28434406>.
67. Achan J, Kakuru A, Ikilezi G, et al. Growth recovery among HIV-infected children randomized to lopinavir/ritonavir or NNRTI-based antiretroviral therapy. *Pediatr Infect Dis J*. 2016;35(12):1329-1332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27580060>.
68. Arpadi SM, Shiao S, Strehlau R, et al. Efavirenz is associated with higher bone mass in South African children with HIV. *AIDS*. 2016;30(16):2459-2467. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27427876>.

## Entry and Fusion Inhibitors

Ibalizumab (IBA, Trogarzo)

Maraviroc (MVC, Selzentry)

## Ibalizumab (IBA, Trogarzo) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

**Single-Dose Vial for Intravenous Administration:** 200 mg/1.33 mL (150 mg/mL) in a single-dose vial. Each single-dose vial contains the following inactive ingredients: L-histidine, polysorbate 80, sodium chloride, and sucrose.

### Dosing Recommendations

#### Child and Adolescent Dose:

- The safety and efficacy of using ibalizumab (IBA) in children and adolescents has not been established.

#### Adult Dose:

- A single loading dose infusion of IBA 2,000 mg administered intravenously (IV) over 30 minutes is followed by a maintenance dose of IBA 800 mg administered IV over 15 minutes every 2 weeks.
- Food and Drug Administration approval of IBA is limited to heavily treatment-experienced adults with multidrug-resistant HIV infection who are experiencing treatment failure on their current regimen.
- IBA is used in combination with other antiretroviral drugs.

### Selected Adverse Events

- Diarrhea, dizziness, nausea, rash
- Immune reconstitution inflammatory syndrome
- Potential for immunogenicity in the form of anti-IBA antibodies

### Special Instructions

- The solution in the vial has to be diluted in 0.9% Sodium Chloride Injection and administered by IV infusion.
- Using aseptic technique, withdraw 1.33 mL from each vial and transfer into a 250 mL bag of 0.9% sodium chloride for IV injection. Other IV diluents must not be used.
- Once diluted, the solution should be administered immediately. If not used immediately, the solution can be stored at room temperature for up to 4 hours or refrigerated for up to 24 hours. Refrigerated solution should be allowed to stand at room temperature for at least 30 minutes but no more than 4 hours prior to administration.
- Diluted solution is administered as an IV infusion, not as a bolus or IV push.

### Metabolism/Elimination

- Monoclonal antibodies are metabolized to peptides and amino acids.

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

Ibalizumab (IBA) is a humanized IgG4 monoclonal antibody that blocks HIV entry into CD4 T lymphocytes (CD4). Based on IBA's mechanism of action and target-mediated drug disposition, drug-drug interactions are not expected. However, no drug interaction studies have been conducted.<sup>1</sup>

### Major Toxicities

- *More common:* Rash, diarrhea, headache, nausea, dizziness, depression.<sup>1,2</sup>
- *Less common (more severe):* Immune reconstitution inflammatory syndrome.<sup>1</sup>

## Resistance

HIV has shown reduced susceptibility to IBA, as defined by a decrease in maximum percent inhibition, when HIV loses N-linked glycosylation sites in the V5 loop of glycoprotein 120.<sup>1-3</sup>

Phenotypic and genotypic test results showed no evidence of cross resistance between IBA and any Food and Drug Administration (FDA)-approved classes of antiretroviral (ARV) drugs.<sup>4</sup> IBA exhibits ARV activity against R5-tropic, X4-tropic, and dual-tropic HIV.<sup>4</sup>

## Pediatric Use

### Approval

IBA is not approved by the FDA for use in pediatric patients. IBA was approved by the FDA in 2018 for use in adults in combination with other ARV drugs, with approval limited to heavily treatment-experienced adults with multidrug-resistant HIV who are experiencing treatment failure on their current regimen.<sup>5</sup>

### Efficacy in Clinical Trials

Trial TMB-301 was conducted in 40 adults aged 23 to 65 years 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.<sup>3,5</sup> Participants continued their current ARV regimens and received a 2,000-mg loading dose of IBA on Day 7 of the study. One week after the loading dose, participants optimized their ARV regimens. Participants received IBA 800 mg on Day 21 and every 2 weeks thereafter. At Week 25, 43% of participants achieved suppressed viral loads of <50 copies/mL.<sup>1,3</sup> At Week 48 of an open-label extension study, 24 participants were taking IBA and their optimized ARV regimen. Sixteen of 27 participants (59%) had viral loads <50 copies/mL at 48 weeks.<sup>6,7</sup>

### Mechanism of Action

IBA is a recombinant humanized monoclonal antibody that blocks HIV from infecting CD4 cells. It does this by binding to domain 2 of the CD4 receptor, which interferes with the post-attachment steps that allow HIV virus particles to enter host cells and prevents the viral transmission that occurs via cell-cell fusion.<sup>1,7</sup> Since IBA 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.

## References

1. Ibalizumab [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/761065lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761065lbl.pdf).
2. Jacob SA, Jacob DG. Ibalizumab targeting CD4 receptors, an emerging molecule in HIV therapy. *Front Microbiol.* 2017;8:2323. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29230203>.
3. Emu B, Fessel J, Schrader S, et al. Phase 3 Study of ibalizumab for multidrug-resistant HIV-1. *N Engl J Med.* 2018;379(7):645-654. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30110589>.
4. Weinheimer S, Cohen Z, Marsolais C, Lewis S. Ibalizumab susceptibility in patient HIV isolates resistant to antiretrovirals. Abstract 561. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/ibalizumab-susceptibility-patient-hiv-isolates-resistant-antiretrovirals>.
5. Food and Drug Administration. Drug approval package: Trogarzo injection (ibalizumab-uiyk). 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/TROGARZO\\_761065\\_TOC.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/TROGARZO_761065_TOC.cfm).
6. Emu B, Fessel J, Schrader S, et al. Forty-eight-week safety and efficacy on-treatment analysis of ibalizumab in patients with multi-drug resistant HIV-1. *Open Forum Infect Dis.* 2017;4(Suppl 1):S38-S39. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5632088/>.
7. Gulick RM. Investigational antiretroviral drugs: what is coming down the pipeline. *Top Antivir Med.* 2018;25(4):127-132. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29689540>.

# Maraviroc (MVC, Selzentry) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Oral Solution:** 20 mg/mL

**Tablets:** 25 mg, 75 mg, 150 mg, 300 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Maraviroc (MVC) is not approved by the Food and Drug Administration (FDA) for use in neonates or infants.

### Pediatric Dose:

- MVC is approved by the FDA for use in ART-experienced children aged  $\geq 2$  years and weighing  $\geq 10$  kg **who have CCR5-tropic HIV-1**.

### Recommended Maraviroc Dose for Treatment-Experienced Children Aged $\geq 2$ Years and Weighing $\geq 10$ kg: Tablets or Oral Solution

Weight Band	Twice-Daily Dosing	Oral Solution 20 mg/mL	Tablets
Recommended doses when MVC is given with potent cytochrome P450 (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including all protease inhibitors (PIs) 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 to 80 mg	4 mL	One 75-mg tablet
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
$\geq 40$ kg	150 mg	7.5 mL	One 150-mg tablet
Recommended doses when MVC is given with non-interacting drugs, such as nucleoside reverse transcriptase inhibitors (NRTIs), nevirapine (NVP), enfuvirtide (T-20), TPV/r, and raltegravir (RAL)			
10 kg to <20 kg	<b>Not recommended.</b> Data are insufficient to make dosing recommendations for children weighing <30 kg and receiving non-interacting medications.		
20 kg to <30 kg			
30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet
$\geq 40$ kg	300 mg	15 mL	One 300-mg tablet
Recommended doses when MVC is given with potent CYP3A inducers (without a potent CYP3A inhibitor), including efavirenz (EFV) and etravirine (ETR)			
Children in all weight bands	<b>Not recommended.</b> Data are insufficient to make dosing recommendations.		

## Selected Adverse Events

- Nausea, vomiting
- Abdominal pain, diarrhea
- Cough
- Upper respiratory tract infections
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally seen in patients with severe renal insufficiency)
- Dizziness

## Special Instructions

- MVC is recommended for use in patients who only have CCR5-tropic HIV-1. Before using MVC, conduct testing with an HIV tropism assay (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)) to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use MVC if CXCR4-tropic or mixed/dual-tropic HIV is present.
- MVC can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering MVC to patients with underlying cardiac disease.

## Metabolism/Elimination

- MVC is a substrate of CYP3A4. If a patient is receiving antiretroviral agents or other medications that act as CYP3A inducers or inhibitors, the dose of MVC should be adjusted accordingly.

## Maraviroc Dosing in Patients with Hepatic Impairment:

- Use caution when administering MVC to patients with hepatic impairment; MVC concentrations may be increased in these patients.

### 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, T-20, TPV/r, NVP, and RAL	300 mg twice daily
Potent CYP3A inducers (without a potent CYP3A inhibitor), including EFV and ETR	600 mg twice daily

### Maraviroc Dosing in Patients with Renal Impairment:

- There are no data to recommend specific doses of MVC for pediatric patients with mild or moderate renal impairment. MVC is **contraindicated** for pediatric patients with severe renal impairment or end-stage renal disease who are on regular hemodialysis and who are receiving potent CYP3A inhibitors.
- Refer to the manufacturer's prescribing information for the appropriate doses to use in adult patients with renal impairment.

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

- **Absorption:** Absorption of maraviroc (MVC) 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 MVC. Therefore, MVC can be given with or without food.
- **Metabolism:** MVC is a cytochrome P450 (CYP) 3A and p-glycoprotein (P-gp) substrate and requires dose adjustments when administered with medications that modulate CYP3A or P-gp. A patient's medication profile should be carefully reviewed for potential drug interactions before MVC is administered; recommended MVC doses are based on concomitant medications and their anticipated effect on MVC metabolism.

### Major Toxicities

- **More common:** Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, vomiting, diarrhea, and headache. Dizziness occurred in 12.2% of adults but only 3.2% of children when MVC was administered twice daily.
- **Less common (more severe):** Hepatotoxicity has been reported; some cases were preceded by evidence of a systemic allergic reaction (including pruritic rash, eosinophilia, or elevated levels of immunoglobulin). Serious adverse events (AEs) occurred in <2% of MVC-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

### Resistance

An HIV tropism assay should be performed before MVC is administered to a patient. Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

### Pediatric Use

#### Approval

MVC is approved by the Food and Drug Administration for use in treatment-experienced children aged  $\geq 2$  years and weighing  $\geq 10$  kg who have CCR5-tropic HIV-1.<sup>1</sup> **A study of MVC dosing in neonates and infants is currently underway (ClinicalTrials.gov identifier NCT02778204). Preliminary data have been presented.**<sup>2</sup>

### *Pharmacokinetics and Efficacy*

The pharmacokinetics, safety, and efficacy of MVC were examined in an international dose-finding and efficacy study (A4001031) that involved treatment-experienced children aged 2 years to <18 years and weighing  $\geq 10$  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 MVC 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 MVC in combination with potent CYP3A inhibitors, while 10 participants received MVC with noninteracting medications and only three participants received MVC with CYP3A inducers (without CYP3A inhibitors). The key pharmacologic target (geometric mean  $C_{\text{average}}$  of  $> 100$  ng/mL) was achieved with both the tablet and oral solution formulations of MVC.<sup>3</sup>

From a mean baseline plasma HIV RNA concentration of  $4.4 \log_{10}$  copies/mL, a decrease of  $\geq 1.5 \log_{10}$  occurred in all four age-based cohorts. Only two participants discontinued the study due to AEs. The most common MVC-related AEs through 48 weeks were diarrhea (which occurred in 20.3% of participants), vomiting (19.8%), and upper respiratory infections (16.2%). At Week 48, 48% of participants had HIV RNA  $< 48$  copies/mL.<sup>3</sup> The absolute CD4 T lymphocyte cell count and percentage increased in all four subgroups of the study, with overall median increases of 192 cells/mm<sup>3</sup> (interquartile range [IQR] 92–352 cells/mm<sup>3</sup>) and 4% (IQR 1% to 8%), respectively.

## References

1. Maraviroc [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022128s018.208984s001lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022128s018.208984s001lbl.pdf).
2. Rosebush JC, Best B, Chadwick E, et al. Maraviroc safety & pharmacokinetics in HIV-exposed neonates. Abstract 842. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, Massachusetts. Available at: <https://www.croiconference.org/sessions/maraviroc-safety-pharmacokinetics-hiv-exposed-neonates>.
3. Giaquinto C, Mawela MP, Chokeyhaibulkit K, et al. Pharmacokinetics, safety and efficacy of maraviroc in treatment-experienced pediatric patients infected with CCR5-tropic HIV-1. *Pediatr Infect Dis J*. 2018;37(5):459-465. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29023357>.

## **Integrase Inhibitors**

Bictegravir (BIC)

Dolutegravir (DTG, Tivicay)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

## Bictegravir (BIC) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

Bictegravir is only available in a fixed-dose combination (FDC) tablet.

#### Fixed-Dose Combination Tablet:

- [Biktarvy] Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg

When using FDC tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### [Biktarvy] Bictegravir/Emtricitabine/Tenofovir Alafenamide (TAF)

##### Child (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. Studies are currently being conducted to identify the appropriate dose for this age and weight group.

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

- One tablet once daily with or without food in antiretroviral therapy-naïve 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 mutations associated with resistance to the individual components of Biktarvy.

### Selected Adverse Events

- Diarrhea, nausea, headache

### Special Instructions

- Administer Biktarvy with or without food. See Drug Interactions below for guidance when administering Biktarvy with antacids or iron or calcium supplements.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (FTC) or TAF. Severe acute exacerbation of HBV can occur when discontinuing FTC or TAF; therefore, monitor hepatic function for several months after halting therapy with FTC or TAF.
- Biktarvy **is not recommended** for use with other ARV drugs.

### Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P450 3A4 and uridine diphosphate glucuronosyltransferase 1A1.

#### 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 (BIC) 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 the fixed-dose combination (FDC) tablet bictegravir/emtricitabine/

tenofovir alafenamide (BIC/FTC/TAF; Biktarvy) and rifampin is **contraindicated**.<sup>1,2</sup>

- *Renal effects:* BIC is an inhibitor of organic cation transporter 2 and multidrug and toxin extrusion protein 1, so it decreases tubular secretion of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate (eGFR) with no change in glomerular function. Drugs that decrease renal function could reduce clearance of FTC.
- *Absorption:* Administering BIC concurrently with antacids lowers the plasma concentrations of BIC. This 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 BIC. For this reason, Biktarvy should be administered at least 2 hours before or 6 hours after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium when Biktarvy is given on an empty stomach. Biktarvy and antacids or supplements that contain calcium or iron can be taken together with food.

### **Major Toxicities**

- *More common:* Diarrhea, nausea, headache. In two clinical trials, total bilirubin increased by up to 2.5 times the upper limit of normal in 12% of patients who received Biktarvy. In general, however, bilirubin increases were quite mild and did not lead to drug discontinuations in these trials.<sup>2</sup> BIC may cause an increase in creatine kinase concentration. **Weight gain has been reported in adults who were receiving Biktarvy (see Table 15h).**
- *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.

### **Pediatric Use**

#### *Approval*

BIC, which is only available as part of the FDC tablet BIC/FTC/TAF (Biktarvy), was approved by the Food and Drug Administration in 2018 for use in adults and in 2019 for use in children or adolescents weighing  $\geq 25$  kg. Biktarvy is approved for patients who have no ARV treatment history, and it 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 mutations associated with resistance to the individual components of the FDC.<sup>2</sup>

#### *Efficacy in Clinical Trials in Adults*

In a short-term Phase 1 study, BIC monotherapy at doses of BIC 50 mg or BIC 100 mg was well tolerated. Three out of eight participants in both of these dosing groups achieved HIV RNA  $< 50$  copies/mL within 11 days.<sup>3</sup> The efficacy (defined as viral load suppression to HIV RNA  $< 50$  copies/mL) and safety (as measured by the incidence of study drug discontinuation or death) of Biktarvy were similar to the efficacy and safety of comparator regimens in two Phase 3 randomized trials in treatment-naïve adults. Viral load suppression occurred in 89% of participants who received coformulated BIC 50 mg/FTC 200 mg/TAF 25 mg ( $n = 320$ ) and in 93% of participants who received a regimen of dolutegravir (DTG) 50 mg plus FTC 200 mg plus TAF 25 mg ( $n = 325$ ). Study drug discontinuation occurred in 1% of participants in both groups.

In a separate trial, viral load suppression occurred in 92% of participants who received BIC/FTC/TAF ( $n = 314$ ) and in 93% of participants who received coformulated abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg (ABC/DTG/3TC) ( $n = 315$ ). Study drug discontinuation was not reported for any of the participants who received BIC/FTC/TAF, though it did occur in 1% of participants who received ABC/DTG/3TC.<sup>2,4</sup>

Studies that randomized virologically suppressed patients who were on stable ARV regimens to either continue their current regimens or switch to coformulated BIC/FTC/TAF have shown that BIC/FTC/TAF has similar safety and efficacy to existing regimens. Viral load suppression occurred in 94% of participants who were randomized to switch to BIC/FTC/TAF (n = 282) and in 95% of participants who continued taking ABC/DTG/3TC (n = 281). Study drug discontinuation was reported in 2% of participants who received BIC/FTC/TAF and 1% of participants who received ABC/DTG/3TC. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (n = 290) achieved viral load suppression, while 89% of participants who continued receiving atazanavir-based or darunavir-based combination ARV regimens (n = 287) achieved viral load suppression. Study drug discontinuation occurred in 1% of participants in both of these groups.<sup>2</sup>

### Pharmacokinetics

Pharmacokinetic (PK) studies of Biktarvy, which contains BIC 50 mg, have been performed in adults, adolescents aged 12 years to <18 years who weigh  $\geq 35$  kg, and children aged 6 years to <12 years who weigh  $\geq 25$  kg. These studies show a higher BIC  $C_{max}$  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 in 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 trough concentrations, which may lead to less “pharmacologic forgiveness” in persons with lower adherence (see Table B below).<sup>5</sup>

**Table A. Bictegravir Pharmacokinetics in Children, Adolescents, and Adults with HIV**

PK Parameters	Children	Adolescents	Adults <sup>2</sup>
	Aged 6 Years to <12 Years and Weighing $\geq 25$ kg <sup>6</sup>	Aged 12 Years to <18 Years and Weighing $\geq 35$ kg <sup>7</sup>	
Dose (mg)	50	50	50
Dose for Lowest Weight in the Cohort (mg/kg)	2	1.43	1.25a
AUC <sub>tau</sub> ng•h/mL Mean (CV%)	121,000 (36)	109,668 (31)	102,000 (26.9)
C <sub>max</sub> ng/mL Mean (CV%)	11,000 (28)	8,087 (30)	6,150 (22.9)
C <sub>tau</sub> ng/mL Mean (CV%)	2,370 (79)	2,327 (49)	2,610 (35)

<sup>a</sup> This dose was calculated using 40 kg as the lowest weight for adults.

**Key:** AUC<sub>tau</sub> = area under the concentration time curve over the dosing interval; C<sub>max</sub> = maximum serum concentration; C<sub>tau</sub> = trough serum concentration at the end of the dosing interval; CV = coefficient of variation; PK = pharmacokinetic

**Table B. Bictegravir Pharmacokinetics in Children and Adolescents with HIV**

Cohort Characteristics	Dose (mg)	Dose for Lowest Weight in Cohort (mg/kg)	GMR% (90% CI) Compared to Adult Values <sup>a</sup>		
			AUC <sub>tau</sub>	C <sub>max</sub>	C <sub>tau</sub>
Aged 6 Years to <12 Years and Weighing ≥25 kg <sup>6</sup>	50	2	116 (104–130)	177 (162–194)	78.3 (63.4–96.7)
Aged 12 Years to <18 Years and Weighing ≥35 kg <sup>7</sup>	50	1.43	107 (97–118)	130 (119–143)	86 (74–100)

<sup>a</sup> In this table, child and adolescent PK values are compared to the PK values of adults who received BIC 50 mg. The dose for the lowest weight in the adult cohort was 1.25 mg/kg; this was calculated using 40 kg as the lowest weight for adults.

**Key:** AUC<sub>tau</sub> = area under the concentration time curve over the dosing interval; BIC = bictegravir; CI = confidence interval; C<sub>max</sub> = maximum serum concentration; C<sub>tau</sub> = 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*

BIC 50 mg/FTC 200 mg/TAF 25 mg (Biktarvy) 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 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<sub>max</sub> for BIC were similar in adolescents and adults, the mean BIC trough concentration in adolescents aged 12 years to <18 years was 2,327 ng/mL (with a coefficient of variation [CV] of 49%); in adults, the mean BIC trough concentration was 2,610 ng/mL (CV 35%). The geometric mean ratio of the adolescent/adult trough concentration was 86% (90% CI, 74% to 100%). All 24 participants in the study had viral loads <50 copies/mL at Week 24.<sup>7</sup>

#### *Use of Biktarvy in Children Aged 6 Years to <12 Years*

BIC 50 mg/FTC 200 mg/TAF 25 mg was administered to children aged 6 years to <12 years who weighed ≥25 kg and who had had viral loads <50 copies/mL for ≥6 months on their current ARV regimens. Despite a high AUC and C<sub>max</sub>, the drug combination was well tolerated, with a fall in eGFR similar to that seen in adult studies. 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<sub>min</sub> is compared to adult values (Table B), although population PK modeling suggests a C<sub>min</sub> comparable to adult values.<sup>8</sup> 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.<sup>6</sup>

The two studies described above were combined and carried to 48 weeks, at which time 74 of 75 participants had viral loads <50 copies/mL.<sup>8</sup>

## References

1. Custodio JM, West SK, Collins S, et al. Pharmacokinetics of bictegravir administered twice daily in combination with rifampin. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/pharmacokinetics-bictegravir-administered-twice-daily-combination-rifampin>.
2. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/210251s006lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210251s006lbl.pdf).
3. Gallant JE, Thompson M, DeJesus E, et al. Antiviral activity, safety, and pharmacokinetics of bictegravir as 10-day

monotherapy in HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;75(1):61-66. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28196003>.

4. Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet*. 2017;390(10107):2063-2072. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28867497>.
5. Shuter J. Forgiveness of non-adherence to HIV-1 antiretroviral therapy. *J Antimicrob Chemother*. 2008;61(4):769-773. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18256112>.
6. Cotton M, Liberty A, Rodriguez CA, et al. Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in HIV-1-infected children (6 to < 12 years). Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_39.htm](http://www.natap.org/2018/IAC/IAC_39.htm).
7. Gaur A, Rodriguez C, McGrath EJ, et al. Bictegravir/FTC/TAF single-tablet regimen in adolescents: week 24 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2018. Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/bictegravirftctaf-single-tablet-regimen-adolescents-week-24-results>.
8. Gaur A, Cotton M, Rodriguez C, et al. Bictegravir/FTC/TAF single-tablet regimen in adolescents & children: Week 48 results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington. Available at: <http://www.croiwebcasts.org/p/2019croi/46>

## Dolutegravir (DTG, Tivicay) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

**Tablets:** 10 mg, 25 mg, 50 mg

#### Fixed-Dose Combination Tablets:

- [Dovato] Dolutegravir 50 mg/lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg/rilpivirine 25 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Neonate and Infant Dose:

- Dolutegravir (DTG) is not approved for use in neonates or infants.

#### Child (Weighing <20 kg) Dose:

- No dosing recommendations can be made for children weighing <20 kg.

#### Child and Adolescent (Weighing ≥20 kg to <40 kg) Dose:

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using an investigational dose of DTG 50 mg once daily for children and adolescents weighing ≥20 kg who are antiretroviral therapy (ART)-naïve or ART-experienced (but integrase strand transfer inhibitor [INSTI]-naïve) and who are not being treated with uridine diphosphate glucuronyl transferase (UGT) 1A1 or cytochrome P450 (CYP) 3A inducers or inhibitors.
- DTG is not approved by the Food and Drug Administration (FDA) for use in children weighing <30 kg. However, interim data from ongoing trials indicate that using the FDA-approved dose of DTG 35 mg in patients weighing ≥30 kg to 40 kg may result in suboptimal trough concentrations, and additional data supports the 50-mg dose recommended by the Panel (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).

### 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

- DTG may be taken without regard to meals.
- DTG should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications.
- 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**.<sup>1</sup>
- The efficacy of DTG 50 mg twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see the Resistance section below).

### Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose

Population	Recommended Dose
ARV-naive or ARV-experienced/ INSTI-naive patients	DTG 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	DTG 50 mg twice daily <sup>a</sup>
INSTI-experienced patients with any INSTI-associated resistance mutations or clinically suspected INSTI resistance	DTG 50 mg twice daily <sup>a,b</sup>

<sup>a</sup> The 50-mg, twice-daily dose **should not be used** in patients weighing  $< 40$  kg.

<sup>b</sup> These patients should receive drug combinations that do not include metabolic inducers when possible.

### [Dovato] Dolutegravir/Lamivudine

#### Adult Dose:

- One tablet once daily with or without food as a complete regimen in ARV-naive adults with no known mutations associated with resistance to the individual components of Dovato.
- Dovato is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen. However, it could be used as part of a three-drug regimen in patients who meet the minimum body weight requirements for each component drug (see the Simplification of Treatment section below).

### [Juluca] Dolutegravir/Rilpivirine

#### Adult Dose:

- One tablet once daily with a meal as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Juluca.
- Juluca is not approved by the FDA or recommended by the Panel for use in children or adolescents as a complete regimen (see the Simplification of Treatment section below).

### [Triumeq] Abacavir/Dolutegravir/Lamivudine

#### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose:

- One tablet once daily with or without food.
- For use in patients who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not

- Patients should be tested for hepatitis B virus (HBV) infection prior to use of Triumeq or Dovato. Lamivudine (3TC)-resistant HBV variants have been reported in patients who received 3TC-containing ARV regimens. Patients with HBV/HIV coinfection who receive Dovato will require additional treatment for chronic HBV infection. Severe exacerbation of hepatitis can occur in patients with HBV/HIV coinfection who discontinue 3TC.

### Metabolism/Elimination

- UGT1A1 and CYP3A substrate. Drugs that induce these enzymes and transporters may decrease plasma concentrations of DTG. Drugs that inhibit these enzymes may increase DTG plasma concentrations.

### Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Due to a lack of data, DTG **is not recommended** for use in patients with severe hepatic impairment.
- DTG 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 DTG with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance  $< 30$  mL/min), because DTG concentrations will be decreased. The cause of this decrease is unknown.

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  $\geq 40$  kg is one tablet once daily.

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

- *Metabolism:* Dolutegravir (DTG) is a uridine diphosphate glucuronyl transferase (UGT) 1A1 and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A-modulating or CYP3A-modulating medications. Because etravirine (ETR) significantly reduces plasma concentrations of DTG, DTG **should not be administered** with ETR without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this effect on DTG concentrations. DTG **should not be administered** with nevirapine because of insufficient data on interactions between these drugs.
- Atazanavir (ATV) is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients who were receiving DTG, patients who also received ATV had plasma concentrations of DTG that were two-fold to four-fold higher than those of patients who received other antiretroviral (ARV) drugs.<sup>2</sup>
- Before administering DTG, clinicians should carefully review a patient's medication profile for potential drug interactions.

**Major Toxicities**

- *More common:* Insomnia and headache. **Weight gain has been reported in adults who received DTG (see Table 15h—Lyodystrophies and Weight Gain).**
- *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 that neuropsychiatric adverse effects (AEs) have occurred after initiation of DTG-based therapy in adults.<sup>3,4</sup>
- *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 strand transfer inhibitors (INSTIs), particularly DTG.<sup>5,6</sup> This phenomenon is presumed to be linked to the rapid decline in HIV RNA observed in patients receiving INSTI-based therapy.
- *Rare:* Hepatotoxicity has been reported; two cases of liver injury were presumed to be related to the use of DTG. One of these cases required liver transplantation.<sup>7,8</sup>
- *Rare:* A single case of drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) has been reported.<sup>9</sup>
- *Rare:* In a prospective surveillance study of birth outcomes among pregnant women on antiretroviral therapy (ART) in Botswana, a small but significant increase in the risk of neural tube defects (NTDs) has been observed among infants born to women who were receiving DTG at the time of conception.<sup>10</sup> Before patients become sexually active, pediatric and adolescent providers should discuss the potential risk of NTDs with patients who are receiving or initiating DTG and their caregivers so that they can make informed decisions about its use **(see Appendix D. Dolutegravir Counseling Guide for Health Care**

**Providers** in the Perinatal Guidelines). 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 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 DTG 50 mg twice daily is reduced in patients with the INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

### Pediatric Use

#### Approval

DTG is approved by the Food and Drug Administration (FDA) for use in combination with other ARV drugs in children and adolescents weighing  $\geq 30$  kg who are treatment-naive or treatment-experienced but INSTI-naive at DTG doses that are lower than the adult dose. However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using the adult dose in children and adolescents weighing  $\geq 20$  kg (see [Appendix A, Table 2](#)).<sup>11</sup> The World Health Organization (WHO) also recommends using DTG at the adult dose of DTG 50 mg in children weighing  $\geq 20$  kg.<sup>12</sup> These recommendations are based on pharmacokinetic (PK) and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY) that are described below. The combination tablet abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; Trimeq) is approved by the FDA for use in children and adolescents weighing  $\geq 40$  kg, although the Panel recommends using it in children and adolescents weighing  $\geq 25$  kg (see [Appendix A, Table 2](#)).<sup>13</sup> The combination tablets dolutegravir/rilpivirine (DTG/RPV; Juluca) and dolutegravir/lamivudine (DTG/3TC; Dovato) are not approved by the FDA for use in children or adolescents at the time of this review,<sup>14,15</sup> and the Panel **does not recommend** using these drugs.

**Table A. Comparison of Food and Drug Administration, European Medicines Agency, World Health Organization, and Panel Dosing Recommendations for Dolutegravir Film-Coated Tablets**

Body Weight	FDA-Recommended Dose <sup>a</sup>	EMA-Recommended Dose <sup>a</sup>	WHO-Recommended Dose <sup>a</sup>	Panel-Recommended Dose <sup>a</sup>
15 kg to <20 kg	NRS	20 mg <sup>b</sup>	NRS	NRS
20 kg to <30 kg	NRS	25 mg	50 mg <sup>d</sup>	50 mg <sup>d</sup>
30 kg to <40 kg	35 mg <sup>c</sup>	35 mg <sup>c</sup>	50 mg <sup>d</sup>	50 mg <sup>d</sup>
$\geq 40$ kg	50 mg	50 mg	50 mg	50 mg

<sup>a</sup> All doses are administered once daily.

<sup>b</sup> Administered as two 10-mg film-coated tablets.

<sup>c</sup> Administered as one 25-mg film-coated tablet and one 10-mg film-coated tablet.

<sup>d</sup> Weight categories have been altered to fit this table. Both WHO and the Panel recommend DTG 50 mg for children weighing 20 kg to <40 kg.

**Key:** DTG = dolutegravir; EMA = European Medicines Agency; FDA = Food and Drug Administration; NRS = no recommendation specified; Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; WHO = World Health Organization

### Formulation Differences: Film-Coated Tablet Compared to Dispersible Tablet

DTG is currently available as a film-coated tablet. A dispersible tablet has been developed and is being studied for use in those who cannot swallow tablets. The dispersible tablet has 60% to 80% greater bioavailability in adults than the film-coated tablet,<sup>16</sup> so doses studied using the dispersible tablet cannot be

directly compared to those using the film-coated tablet. The drug exposure of the 50-mg film-coated tablet is approximately equal to the drug exposure of DTG 30 mg administered as dispersible tablets. A previously investigated DTG granule formulation is no longer being studied.<sup>17</sup>

### ***Efficacy and Pharmacokinetics***

#### *Children and Adolescents Aged $\geq 12$ Years and Weighing $\geq 40$ kg*

IMPAACT P1093 is an ongoing, open-label trial of DTG in children with HIV. Initial FDA approval of DTG for use in adolescents weighing  $\geq 40$  kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.<sup>18</sup> Intensive PK evaluations were performed on the first 10 participants, nine of whom weighed  $\geq 40$  kg and received DTG 50 mg and one of whom weighed 37 kg and received DTG 35 mg. These doses resulted in exposures that were comparable to those seen in adults who received DTG 50 mg once daily. Nine of 10 participants achieved HIV RNA levels  $< 400$  copies/mL at Week 4 (optimal background therapy was added 5–10 days after DTG 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 levels  $< 50$  copies/mL. No safety or tolerability concerns were identified. By Week 144, 39% and 30% of participants had achieved HIV RNA levels  $< 400$  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 retrospective, multicenter French cohort study that evaluated 50 adolescents who initiated DTG-based ART. Of 17 adolescents who were virologically suppressed at the time of DTG-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 DTG, 19 (58%) achieved sustained virologic success. Overall, 66% of patients achieved sustained virologic suppression and 78% had undetectable plasma viral loads by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and were more likely to have detectable viremia in the 6 months prior to DTG initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued DTG-based treatment because of a significant AE (dizziness and sleep disturbance).<sup>19</sup>

Another cohort of adolescents in Barcelona received the fixed-dose combination (FDC) product ABC 600 mg/DTG 50 mg/3TC 300 mg (Triumeq). Of the twelve patients described, one received Triumeq for initial ART, six received Triumeq for treatment simplification, and five received Triumeq because of previous treatment failure. Nine of the 12 patients achieved or maintained viral suppression after switching to Triumeq; three patients failed to achieve suppression due to suboptimal adherence. Of note, patients complained about the size of the tablet, and six patients reported having to crush or split the tablet in order to swallow it (see [Appendix A, Table 2](#)).<sup>20</sup>

#### *Children and Adolescents Aged $< 12$ Years*

A younger cohort of children aged  $\geq 6$  years to  $< 12$  years underwent PK assessment and remains in long-term follow up in IMPAACT P1093, with those weighing  $\geq 30$  kg to  $< 40$  kg receiving DTG 35 mg and those weighing  $\geq 40$  kg receiving DTG 50 mg. At 48 weeks, data from 23 participants demonstrated a favorable safety profile, adequate PKs, and virologic efficacy, with HIV RNA levels of  $< 50$  copies/mL achieved in 17 of 23 participants (74%).<sup>18,21</sup> These data led to FDA approval of the lower-strength, film-coated DTG tablets at a dose of 35 mg for use in children with HIV who weigh  $\geq 30$  kg to  $< 40$  kg. The FDA did not approve a DTG dose for use in children weighing  $< 30$  kg because the PK data in the lower weight bands were limited and the observed  $C_{\text{trough}}$  concentrations in patients in these weight bands were lower than expected.

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 that were approved by the European Medicines Agency (EMA; see Table A above). A total of 674 children aged  $< 18$  years were enrolled; 282 children started DTG as first-line therapy and 392 started DTG as second-line therapy.<sup>22</sup> 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 DTG tablet (n = 27). Children weighing  $\geq 25$  kg who received the 50-mg, film-coated DTG 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 25-mg, film-coated DTG tablet resulted in drug exposures that were lower than the target exposure for adults, particularly  $C_{\text{trough}}$ . The median  $C_{\text{trough}}$  was lower in the 20 kg to <25 kg group than in the 14 kg to <20 kg group.<sup>23,24</sup> Data from ODYSSEY was recently reported on children weighing 20 kg to <25 kg who received either the 50-mg film-coated tablet or 30 mg of DTG administered as six 5-mg dispersible tablets. Both of these doses achieved area under the curve (AUC) and  $C_{\text{max}}$  values that were higher than adult PK reference values, but still acceptable, and both doses achieved  $C_{\text{trough}}$  values that were similar to adult reference values.<sup>25</sup> At this time, neither the FDA nor the EMA have reviewed the data supporting the use of the 50-mg film-coated tablet in children weighing between 20 kg and <40 kg.

The EMA used the IMPAACT P1093 data to inform population PK modelling and simulation analyses to approve the lower-strength, film-coated DTG tablets for use in children aged  $\geq 6$  years and weighing  $\geq 15$  kg.<sup>26</sup> The EMA approved doses of DTG 20 mg for children weighing 15 kg to <20 kg and doses of DTG 25 mg for those weighing 20 kg to <30 kg (see Table A above). As noted, evaluation of these doses during the ODYSSEY study indicated that many children failed to achieve adequate trough concentrations. The Panel **does not recommend** the use of DTG in children weighing <20 kg until further data are available 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 DTG at the EU-licensed doses (see Table A above). Of these 174 children, 53% were female and 91% had perinatally acquired HIV, and the median age was 15.5 years at DTG initiation (interquartile range 13.5–16.7 years). Only 6% of the cohort was treatment-naïve, and 38% had previous exposure to three classes of ARV drugs. Overall, nine participants (5%) discontinued DTG; three discontinued because of toxicity, three discontinued because an alternative regimen was available, and three discontinued for other or unknown reasons. Viral suppression was reported in 80 of 95 participants (84%) who remained on DTG for 6 months, and viral suppression was reported in 41 of 49 participants (84%) who remained on DTG for 12 months. Median changes in CD4 T lymphocyte cell counts were -9 cells/mm<sup>3</sup> at 6 months (n = 81) and +47 cells/mm<sup>3</sup> at 12 months (n = 41) of DTG treatment.<sup>27</sup>

#### *Children Aged <6 Years Who Are Not Able to Swallow Tablets: Dolutegravir Dispersible Tablets*

The first presentation of the data on DTG dispersible tablets reported that three age cohorts of 10 patients ( $\geq 4$  weeks to <6 months,  $\geq 6$  months to <2 years, and  $\geq 2$  years to <6 years) received protocol-defined, weight-based dosing using combinations of 5-mg dispersible tablets. While target AUC<sub>24h</sub> and  $C_{24h}$  levels were achieved in the youngest cohort,  $C_{24h}$  levels were low in children aged 6 months to <6 years. The dispersible tablet formulation was well-tolerated by all age groups. Higher doses are being evaluated in some age/weight groups.<sup>28</sup>

#### ***Simplification of Treatment***

Two trials in adults (SWORD-1 and SWORD-2) supported the approval of a DTG 50 mg/RPV 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 virologically suppressed patients who had been on stable ART for at least 6 months and who had no history of treatment failure or evidence of resistance mutations. The participants were randomized to either receive DTG/RPV or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA levels <50 copies/mL.<sup>29</sup> More AEs were reported and led to discontinuation in the DTG/RPV arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate (TDF), small but statistically significant increases in hip and spine bone mineral density were observed.<sup>30</sup>

The approval of DTG 50 mg/3TC 300 mg (Dovato) as a complete regimen was supported by data from two randomized, double-blind, controlled trials (GEMINI-1 and GEMINI-2) in ARV-naïve adults with HIV. GEMINI-1 and GEMINI-2 are identical, 148-week trials that enrolled a total of 1,433 adults with HIV who had

plasma HIV RNA levels between 1,000 copies/mL and  $\leq 500,000$  copies/mL at screening and no evidence of major resistance mutations or hepatitis B virus infection. Participants were randomized to receive either DTG plus 3TC or DTG plus 3TC/TDF. During 48 weeks of treatment, 91% of patients who received DTG plus 3TC and 93% of patients who received DTG plus 3TC/TDF achieved HIV RNA levels  $< 50$  copies/mL. Similar proportions of patients discontinued treatment due to AEs or other reasons in the two treatment arms.<sup>31</sup>

Although neither Juluca nor Dovato is approved by the FDA for use in adolescents, the doses of the component drugs that make up these FDC tablets are approved for use in adolescents. The Panel usually endorses the use of adult formulations in adolescents, and these products may be appropriate for use in certain adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents, who may have difficulty adhering to therapy, the Panel **does not currently recommend** using two-drug simplification regimens in adolescents and children until more data are available.

### ***Crushing Film-Coated Tablets for Administration***

In patients who have difficulty swallowing whole tablets, the 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**.<sup>1</sup> 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.<sup>32</sup>

## **References**

1. ViiV. Medical Information Response. 2017.
2. Cattaneo D, Minisci D, Cozzi V, et al. Dolutegravir plasma concentrations according to companion antiretroviral drug: unwanted drug interaction or desirable boosting effect? *Antivir Ther*. 2017;22(4):353-356. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28008867>.
3. Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. *AIDS*. 2017;31(13):1853-1858. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28692533>.
4. Fettiplace A, Stainsby C, Winston A, et al. Psychiatric symptoms in patients receiving dolutegravir. *J Acquir Immune Defic Syndr*. 2017;74(4):423-431. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27984559>.
5. Wiiting I, Rokx C, Wit F, et al. Integrase inhibitors are an independent risk factor for IRIS: an ATHENA cohort study. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
6. Dutertre M, Cuzin L, Demonchy E, et al. Initiation of antiretroviral therapy containing integrase inhibitors increases the risk of IRIS requiring hospitalization. *J Acquir Immune Defic Syndr*. 2017;76(1):e23-e26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28418992>.
7. Wang B, Abbott L, Childs K, et al. Dolutegravir-induced liver injury leading to sub-acute liver failure requiring transplantation: a case report and review of literature. *Int J STD AIDS*. 2018;29(4):414-417. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29059031>.
8. Christensen ES, Jain R, Roxby AC. Abacavir/dolutegravir/lamivudine (trumeq)-induced liver toxicity in a human immunodeficiency virus-infected patient. *Open Forum Infect Dis*. 2017;4(3):ofx122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28748198>.
9. Martin C, Payen MC, De Wit S. Dolutegravir as a trigger for DRESS syndrome? *Int J STD AIDS*. 2018;29(10):1036-1038. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29621952>.
10. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in botswana. *N Engl J Med*. 2019;381(9):827-840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31329379>.

11. Dolutegravir [package insert]. Food and Drug Administration. 2019. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/204790s0241bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/204790s0241bl.pdf).
12. World Health Organization. Policy update: update of recommendations on first- and second-line antiretroviral regimens, HIV treatment. 2019. Available at: <https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1>.
13. Abacavir/dolutegravir/lamivudine (Triumeq) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/205551s0221bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205551s0221bl.pdf).
14. Dolutegravir/rilpivirine (Juluca) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/210192s0081bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210192s0081bl.pdf).
15. Dolutegravir/lamivudine (Dovato) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/211994s0001bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211994s0001bl.pdf).
16. Parasrampur R, Adkison K, Wolstenholme A, et al. Comparison of relative bioavailability of tivicay immediate release and dispersible pediatric tablets to immediate release tivicay adult tablets. Presented at: International Workshop on Clinical Pharmacology of Antiviral Therapy. 2018. Baltimore, Maryland.
17. Ruel T, Acosta E, Singh RP, et al. Dolutegravir pharmacokinetics, safety and efficacy in HIV+ children 2 to < 6 years old. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
18. Viani RM, Alvero C, Fenton T, et al. Safety, Pharmacokinetics and efficacy of dolutegravir in treatment-experienced HIV-1 infected adolescents: 48-Week results from IMPAACT P1093. *Pediatr Infect Dis J*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26244832>.
19. Briand C, Dollfus C, Caseris M, et al. Dolutegravir-based cART in vertically HIV-1-infected adolescents , real-world setting. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
20. Bossacoma Busquets F, Noguera-Julian A, Sanchez E, Fortuny C. Dolutegravir plus abacavir/lamivudine works in adolescents, but size matters. *J Antimicrob Chemother*. 2017;72(10):2958-2960. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29091219>.
21. Wiznia A, Alvero C, Fenton T, et al. IMPAACT 1093: dolutegravir in 6- to 12-year-old HIV-infected children: 48-week results. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, Massachusetts.
22. Moore C, Kekitiinwa A, Kaudha E, et al. ODYSSEY: A randomised trial evaluating the efficacy and toxicity of dolutegravir-based antiretroviral therapy compared to standard of care in HIV-infected children starting first-line or second-line therapy: design, current status and baseline characteristics. Presented at: 10th International Workshop on HIV Pediatrics. 2018. Amsterdam, Netherlands.
23. Turkova A, Bollen P, Kaudha E, Chidziva E, Lugemwa A, et al. Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing  $\geq 25$ kg after switching to 50 mg film-coated dolutegravir tablets in the ODYSSEY trial. Presented at: International Workshop on HIV Pediatrics. 2018. Amsterdam, Netherlands.
24. Bollen P, Turkova A, Mujuru HA, Musiime V, Amuge P, et al. Stead-state pharmacokinetics and early safety data in HIV-infected African children weighing 14 to < 25 kg on film-coated dolutegravir 25 mg tablets in the ODYSSEY trial. Presented at: 10th International Workshop on HIV Pediatrics. 2018. Amsterdam, Netherlands.
25. Bollen P, Turkova A, Mujuru H, et al. Adult dolutegravir 50 mg film-coated tablets in children living with HIV weighing 20 to < 25 kg. Presented at: Conference on Retroviruses and Opportunistic Infections. 2019. Seattle, Washington.
26. European Medicines Agency. Summary of product characteristics (tivicay). 2014. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002753/WC500160680.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002753/WC500160680.pdf).
27. Collins I, Crichton S, Gibb D, Judd A, on behalf of the CHIPS Steering Committee. Safety and effectiveness of dolutegravir (DTG) in children and adolescents with HIV in the UK/Ireland. Presented at: International Workshop on HIV Pediatrics. 2018. Amsterdam, Netherlands.
28. Ruel T, Acosta EP, Singh R, et al. Pharmacokinetic and 4-week safety/efficacy of dolutegravir (S/GSKI349572) dispersible tablets in HIV-infected children aged 4 weeks to <6 years: results from IMPAACT PI093. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands. Available at: [http://www.natap.org/2018/IAC/IAC\\_44.htm](http://www.natap.org/2018/IAC/IAC_44.htm).

29. Llibre JM, Hung CC, Brinson C, et al. Phase III SWORD 1&2: switch to DTG+RPV maintains virologic suppression through 48 wks. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.
30. McComsey G, Gonzalez-Garcia J, Lupo S, et al. Sub-study 202094 of SWORD 1 & SWORD 2: switch from TDF containing regimen to DTG+RPV improves bone mineral density and bone turnover markers over 48 weeks. Presented at: International AIDS Society Conference on HIV Science. 2017. Paris, France. Available at: <http://programme.ias2017.org/Abstract/Abstract/5743>.
31. Cahn P, Madero S, Arribas J, et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment-naive adults with HIV-1 infection—48-week results from the GEMINI studies. Presented at: International AIDS Conference. 2018. Amsterdam, Netherlands.
32. Roskam-Kwint M, Bollen P, Colbers A, et al. Crushing of dolutegravir combination tablets increases dolutegravir exposure. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington.

## Elvitegravir (EVG) (Last updated April 14, 2020; last reviewed April 14, 2020)

### 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 10 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg

When using FDC tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### [Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

*Child (Weighing <25 kg) Dose:*

- There are no data on the appropriate dose of Genvoya for children weighing <25 kg.

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

- One tablet once daily with food in antiretroviral therapy (ART)-naive patients. This dose of Genvoya 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 ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.

#### [Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)

*Child and Adolescent (Weighing <35 kg) Dose:*

- There are no data on the appropriate dose of 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 in ART-naive patients. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV RNA <50 copies/mL) on a

### 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, **high-density lipoprotein cholesterol, triglycerides**, and total cholesterol

#### Cobicistat-Specific Adverse Events:

- Benign increases in serum creatinine levels

stable ART regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.

(reductions in estimated glomerular filtration) due to inhibition of tubular secretion of creatinine

## Special Instructions

- Administer both Genvoya and Stribild with food.
- EVG should be administered at least 4 hours before or after antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.
- When using Stribild, which contains TDF, monitor estimated creatinine clearance (CrCl), urine glucose, and urine protein at baseline and every 3 to 6 months while on therapy. In patients who are at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine levels >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine (FTC), TDF, or TAF. Severe acute exacerbation of HBV can occur when FTC, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after stopping therapy with FTC, TDF, or TAF.
- For information on crushing and cutting tablets, please see [this table](#) from Toronto General Hospital.

## Metabolism/Elimination

- EVG is metabolized by cytochrome P450 (CYP) 3A4 and is a modest inducer of CYP2C9.
- EVG 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.

## Elvitegravir Dosing in Patients with Hepatic Impairment:

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

## Elvitegravir Dosing in Patients with Renal Impairment:

- Stribild **should not be initiated** in patients with estimated CrCl <70 mL/min, and it should be discontinued in patients with estimated CrCl <50 mL/min. FTC and TDF require dose adjustments in these patients, and these adjustments cannot be achieved with an FDC tablet.
- Genvoya **should not be initiated** in patients with estimated CrCl <30 mL/min.

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

- *Absorption:* Elvitegravir (EVG) plasma concentrations are lower with concurrent administration of divalent cations because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Because of this, Stribild and Genvoya should be administered at least 4 hours before or after administering antacids and supplements or multivitamins that contain iron, calcium, aluminum, and/or magnesium.<sup>1</sup>
- *Metabolism:* Stribild and Genvoya contain EVG and cobicistat (COBI). EVG is metabolized predominantly by cytochrome P450 (CYP) 3A4, secondarily by uridine diphosphate glucuronyl transferase 1A1/3, and by oxidative metabolism pathways. EVG is a moderate inducer of CYP2C9. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, COBI inhibits the adenosine triphosphate-dependent transporters P-glycoprotein and the breast cancer resistance protein and the organic anion-transporting polypeptides OATP1B1 and OATP1B3. See the [Cobicistat](#) section for a more detailed summary of drug interactions. There is potential for multiple drug interactions when using both EVG and COBI. Neither Stribild nor Genvoya should be administered concurrently with products or regimens that contain ritonavir (RTV), due to the similar effects of COBI and RTV on CYP3A4 metabolism.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (TDF) or emtricitabine (FTC). Concomitant use of nephrotoxic drugs should be avoided when using Stribild. COBI inhibits MATE1, which increases serum creatinine levels up to 0.4 mg/dL from baseline in adults. Significant increases in serum creatinine levels may represent renal toxicity and should be evaluated.

**Major Toxicities**

- *More common:* Nausea, diarrhea, **fatigue, headache,** flatulence.
- *Less common (more severe):* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported in patients receiving nucleoside reverse transcriptase inhibitors, including TDF and FTC. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children who were taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed in patients taking TDF, including a higher incidence of glycosuria, proteinuria, phosphaturia, and/or calciuria; increases in the levels of serum creatinine and blood urea nitrogen; and decreases in serum phosphate levels. Numerous case reports of renal tubular dysfunction have been reported in patients receiving TDF; patients at increased risk of renal dysfunction should be closely monitored if they are being treated with Stribild. **Genvoya, which contains tenofovir alafenamide (TAF), has an improved bone and renal safety profile when compared to Stribild, which contains TDF. However, Genvoya is associated with greater increases in lipid levels than Stribild, according to findings from large-scale clinical trials.**<sup>2</sup>

**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 EVG and raltegravir.<sup>3</sup>

**Pediatric Use**

*Approval*

Stribild (EVG/c/FTC/TDF) is approved by the Food and Drug Administration (FDA) for use in children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg.<sup>4,5</sup> However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends limiting the use of Stribild to adolescents

with sexual maturity ratings (SMRs) of 4 or 5 due to concerns about decreased BMD in pre-pubertal patients.

Genvoya (EVG/c/FTC/TAF) is approved by the FDA for use in children and adolescents weighing  $\geq 25$  kg with any SMR.<sup>2</sup>

### *Efficacy in Clinical Trials*

EVG/c/FTC/TDF was found to be noninferior to a regimen of efavirenz/emtricitabine/TDF (EFV/FTC/TDF)<sup>6</sup> and noninferior to a regimen of atazanavir/ritonavir (ATV/r) plus FTC/TDF in adults at 144 weeks of treatment.<sup>7</sup> In two studies, 1,733 adults were randomly assigned to receive either EVG/c/FTC/TDF or EVG/c/FTC/TAF.<sup>8</sup> After 48 weeks, those receiving EVG/c/FTC/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL;  $P < 0.0001$ ), significantly less proteinuria (median percent change in protein -3% vs. +20%;  $P < 0.0001$ ), and a significantly smaller decrease in BMD at the spine (mean percent change -1.30% vs. -2.86%;  $P < 0.0001$ ) and hip (-0.66% vs. -2.95%;  $P < 0.0001$ ). Larger increases in fasting lipid levels were observed with EVG/c/FTC/TAF than with EVG/c/FTC/TDF; the median increases in levels of total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were all higher in patients who received EVG/c/FTC/TAF.

### *Formulations*

EVG is an integrase strand transfer inhibitor that is metabolized by CYP3A4. EVG must be used in the fixed-dose combination products Stribild<sup>5</sup> or Genvoya,<sup>2</sup> both of which contain COBI (see below). COBI itself does not have antiretroviral (ARV) activity, but it is a CYP3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to RTV.<sup>9</sup>

Stribild is approved by the FDA as a complete ARV regimen for ARV-naive adults and adolescents with HIV aged  $\geq 12$  years and weighing  $\geq 35$  kg. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Stribild.<sup>5</sup> Trials have shown that Stribild is noninferior to regimens that contain FTC plus TDF plus ATV<sup>10,11</sup> or FTC plus TDF plus EFV.<sup>12,13</sup> COBI inhibits renal tubular secretion of creatinine, and serum creatinine will often increase soon after initiating 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.<sup>14</sup> 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.<sup>5</sup> 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.<sup>5</sup>

Genvoya is approved by the FDA as a complete ARV regimen for ARV-naive children with HIV weighing  $\geq 25$  kg. It can also be used to replace the current ARV regimen in those who have been virologically suppressed (HIV RNA  $< 50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known mutations associated with resistance to the individual components of Genvoya.<sup>2</sup> 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.<sup>8</sup> In children aged  $\geq 6$  years and weighing  $\geq 25$  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.<sup>15</sup>

### *Coadministration of Elvitegravir, Cobicistat, and Darunavir*

The combination of Stribild or Genvoya plus darunavir (DRV) may provide a low pill burden regimen

for ART-experienced individuals. However, an unfavorable drug interaction between EVG/c and DRV is possible, and the available data on the magnitude of the interaction are conflicting. There are also conflicting data on the efficacy of the combination in adults.<sup>16-22</sup>

The most rigorous drug interaction study, performed in HIV-seronegative adults, found 21% lower DRV trough concentrations and 52% lower EVG trough concentrations with DRV 800 mg plus EVG/c 150 mg/150 mg once daily compared to administration of either darunavir/cobicistat 800 mg/150 mg once daily or EVG/c 150 mg/150 mg once daily alone.<sup>16</sup> The actual trough values were 1,050 ng/mL for DRV and 243 ng/mL for EVG.

Despite the findings of the aforementioned drug interaction study in HIV-seronegative adults, the most rigorous efficacy evaluation found that among 89 treatment-experienced adults who were receiving five-tablet ARV regimens, 96.6% achieved virologic suppression (HIV RNA <50 copies/mL) 24 weeks after simplifying their regimens to a two-tablet regimen of Genvoya plus DRV 800 mg once daily.<sup>20</sup> Intensive PK sampling was performed in 15 of these patients (17%). Mean DRV and EVG troughs were 1,250 ng/mL and 464 ng/mL, respectively.

Given the uncertainty around the true magnitude of the drug interaction and the absence of data in children, this combination should be used with caution in children.

#### *Use of Elvitegravir as Genvoya in Children Weighing <25 kg*

Genvoya is not approved to treat children weighing <25 kg.<sup>2,5</sup> 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 Weighing $\geq 25$ kg*

Genvoya is approved by the FDA to treat children with any SMR who weigh  $\geq 25$  kg;<sup>2</sup> this approval was based on 24 weeks of data in 23 children.<sup>23</sup> 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 a concerning decline in CD4 T lymphocyte (CD4) cell counts was observed in these 23 children over the first 24 weeks of Genvoya treatment. CD4 counts declined by a median of 130 cells/mm<sup>3</sup> (with a range of -472 cells/mm<sup>3</sup> to 266 cells/mm<sup>3</sup>) from baseline. However, after enrolling additional children (for a total of 52 participants), the median CD4 count decline at 48 weeks was 25 cells/mm<sup>3</sup>.<sup>24</sup> The mechanism for the reduction in CD4 count 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 counts.<sup>25</sup>

#### *Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 Years and Weighing $\geq 35$ kg*

Studies of the use of Stribild and Genvoya in children with HIV aged  $\geq 12$  years and weighing  $\geq 35$  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.<sup>5</sup> 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.<sup>2</sup> Stribild is not approved to treat children weighing <35 kg.<sup>5</sup>

## References

1. Ramanathan S, Shen G, Hinkle J, Enejosa J, Kearney B. Pharmacokinetic evaluation of drug interactions with ritonavir-boosted HIV integrase inhibitor GS-9137 (elvitegravir) and acid-reducing agents. International Workshop on Clinical Pharmacology of HIV Therapy. 2007. Budapest, Hungary.
2. Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/207561s023lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/207561s023lbl.pdf)
3. Garrido C, Villacian J, Zahonero N, et al. Broad phenotypic cross-resistance to elvitegravir in HIV-infected patients

failing on raltegravir-containing regimens. *Antimicrob Agents Chemother.* 2012;56(6):2873-2878. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22450969>.

4. Elvitegravir [package insert]. Food and Drug Administration. 2015. Available at [http://www.gilead.com/~media/files/pdfs/medicines/hiv/vitekta/vitekta\\_pi.pdf?la=en](http://www.gilead.com/~media/files/pdfs/medicines/hiv/vitekta/vitekta_pi.pdf?la=en).
5. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (Stribild) [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/203100s034lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203100s034lbl.pdf).
6. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr.* 2014;65(3):e118-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24256630>.
7. Clumeck N, Molina JM, Henry K, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. *J Acquir Immune Defic Syndr.* 2014;65(3):e121-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24346640>.
8. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, Phase 3, non-inferiority trials. *Lancet.* 2015;385(9987):2606-2615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25890673>.
9. Tybost [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/203094s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203094s014lbl.pdf)
10. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, Phase 3, non-inferiority trial. *Lancet.* 2012;379(9835):2429-2438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22748590>.
11. Rockstroh JK, DeJesus E, Henry K, et al. A randomized, double-blind comparison of co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr.* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23337366>.
12. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet.* 2012;379(9835):2439-2448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22748591>.
13. Zolopa A, Sax PE, DeJesus E, et al. A randomized double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: analysis of week 96 results. *J Acquir Immune Defic Syndr.* 2013;63(1):96-100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23392460>.
14. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr.* 2012;61(1):32-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22732469>.
15. Sharma S, Gupta S, Majeed S, et al. Exposure-safety of tenofovir in pediatric HIV-infected participants: comparison of tenofovir alafenamide & tenofovir disoproxil fumarate. Abstract 23. International Workshop on HIV Pediatrics. 2018. Amsterdam, Netherlands. Available at: [http://regist2.virology-education.com/abstractbook/2018/abstractbook\\_10ped.pdf](http://regist2.virology-education.com/abstractbook/2018/abstractbook_10ped.pdf).
16. Ramanathan S, Wang H, Szwarcberg J, Kearney BP. Safety/tolerability, pharmacokinetics, and boosting of twice-daily cobicistat administered alone or in combination with darunavir or tipranavir. Abstract P-08. International Workshop on Clinical Pharmacology of HIV Therapy. 2012. Barcelona, Spain. Available at: [http://www.natap.org/2012/pharm/Pharm\\_28.htm](http://www.natap.org/2012/pharm/Pharm_28.htm).

17. Diaz A, Moreno A, Gomez-Ayerbe C, et al. Role of EVG/COBI/FTC/TDF (Quad) plus darunavir regimen in clinical practice. International AIDS Conference. 2016. Durban, South Africa, Available at: <http://programme.aids2016.org/Abstract/Abstract/4927>.
18. Gutierrez-Valencia A, Benmarzouk-Hidalgo OJ, Llaves S, et al. Pharmacokinetic interactions between cobicistat-boosted elvitegravir and darunavir in HIV-infected patients. *J Antimicrob Chemother*. 2017;72(3):816-819. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27999051>.
19. Harris M, Ganase B, Watson B, Harrigan PR, Montaner JSG, Hull MW. HIV treatment simplification to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) plus darunavir: a pharmacokinetic study. *AIDS Res Ther*. 2017;14(1):59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29096670>.
20. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193-200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27753684>.
21. Naccarato MJ, Yoong DM, Fong IW, Gough KA, Ostrowski MA, Tan DHS. Combination therapy with tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat plus darunavir once daily in antiretroviral-naive and treatment-experienced patients: a retrospective review. *J Int Assoc Provid AIDS Care*. 2018;17:2325957417752260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29385867>.
22. Ricard F, Wong A, Lebouche B, et al. Low darunavir concentrations in patients receiving Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) and darunavir once daily. Abstract 50. International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy. 2015. Washington, DC. Available at: [http://regist2.virology-education.com/abstractbook/2015\\_4.pdf](http://regist2.virology-education.com/abstractbook/2015_4.pdf).
23. Natukunda E, Gaur A, Kosalaraksa P, et al. Safety, efficacy, and pharmacokinetics of single-tablet elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in virologically suppressed, HIV-infected children: a single-arm, open-label trial. *Lancet Child Adolescent Health*. 2017;1(1):27-34. Available at: <http://www.sciencedirect.com/science/article/pii/S2352464217300093?via%3Dihub>.
24. Rakhmanina N, Natukunda E, Kosalaraksa P, Batra J, Gaur A, et al. Safety and efficacy of E/C/F/TAF in virologically suppressed, HIV-infected children through 96 weeks. Abstract 22. International Workshop on HIV Pediatrics. 2019. Mexico City, Mexico.
25. Bell T, Baylor M, Rhee S, et al. FDA analysis of CD4+ cell count declines observed in HIV-infected children treated with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Infectious Disease Week 2018. 2018. San Francisco, California. Available at: <https://idsa.confex.com/idsa/2018/webprogram/Paper69959.html>.

# Raltegravir (RAL, Isentress) (Last updated April 14, 2020; last reviewed April 14, 2020)

## Formulations

**Tablet:** 400 mg (film-coated poloxamer tablet)

**High-Dose (HD) Tablet:** 600 mg (film-coated poloxamer tablet)

**Chewable Tablets:** 100 mg (scored) and 25 mg

**Granules for Oral Suspension:** Single-use packet of 100 mg of raltegravir, suspended in 10 mL of water for a final concentration of 10 mg/mL.

**Film-coated tablets, chewable tablets, and oral suspension are not interchangeable.**

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

## Dosing Recommendations

**Note:** No dosing information is available for preterm infants or infants weighing <2 kg at birth. See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or HIV Infection](#) and [Table 12](#) for information about using raltegravir (RAL) for the prevention of perinatal HIV transmission.

### Neonate (Weighing $\geq 2$ kg) Dose:

- RAL is metabolized by uridine diphosphate glucuronyl transferase (UGT1A1), and enzyme activity is low at birth; enzyme activity increases rapidly during the next 4 to 6 weeks of life.

### Raltegravir Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks

Neonates Aged  $\geq 37$  Weeks and Weighing  $\geq 2$  kg:

Weight	Volume (Dose) of Suspension
<b>Birth to 1 Week of Age: Once-Daily Dosing</b>	<b>Approximately 1.5 mg/kg per dose</b>
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
<b>1–4 Weeks of Age: Twice-Daily Dosing</b>	<b>Approximately 3 mg/kg per dose</b>
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 RAL 2 hours to 24 hours prior to delivery, the neonate's first dose should be delayed until 24 hours to 48 hours after birth.

### Infant and Child (Weighing $\geq 3$ kg to <20 kg) Dose:

- For children weighing 11 kg to 20 kg, either oral suspension or chewable tablets can be used.

## Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache, dizziness, fatigue
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

## Special Instructions

- RAL can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any RAL formulations.
- Significant drug interactions are more likely to occur when the RAL HD formulation is used once daily. **The following drugs should not be coadministered with once daily RAL HD dosing:** calcium carbonate, 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<sup>a</sup>

**Note:** The maximum dose of oral suspension is 10 mL (RAL 100 mg) twice daily.

Weight	Twice-Daily Volume (Dose) of Suspension
3 kg to <4 kg	2.5 mL (25 mg)
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)

<sup>a</sup> The weight-based dose recommendation for the oral suspension is based on a dose of approximately RAL 6 mg/kg per dose twice daily.

## Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and High-Dose Tablets

*Children Weighing ≥ 11 kg*

Weighing <25 kg:

- Chewable tablets twice daily. See the table below for chewable tablet doses.

Weighing ≥25 kg:

- RAL 400-mg, film-coated tablets twice daily **or** chewable tablets twice daily. See the table below for chewable tablet doses.

*Children and Adolescents Weighing ≥40 kg:*

- Two RAL 600-mg HD tablets (1,200 mg) once daily
- This dose is for antiretroviral therapy-naïve or virologically suppressed patients who are on an initial dose of RAL 400 mg twice daily.

## Chewable Tablet Dosing Table<sup>a</sup>

**Note:** The maximum dose of chewable tablets is RAL 300 mg twice daily.

Weight	Twice-Daily Dose	Number of Chewable Tablets
11 kg to <14 kg	RAL 75 mg	3 tablets (25 mg) twice daily
14 kg to <20 kg	RAL 100 mg	1 tablet (100 mg) twice daily
20 kg to <28 kg	RAL 150 mg	1 ½ tablets <sup>b</sup> (100 mg) twice daily
28 kg to <40 kg	RAL 200 mg	2 tablets (100 mg) twice daily
≥40 kg	RAL 300 mg	3 tablets (100 mg) twice daily

<sup>a</sup> The weight-based dose recommendation for the chewable tablet is based on a dose of approximately RAL 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, a component of aspartame. Phenylalanine can be harmful to patients with phenylketonuria, and the necessary dietary adjustments should be made in consultation with a metabolic specialist.
- The oral suspension comes in a kit that includes mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document. Each single-use foil packet contains 100 mg of RAL, which will be suspended in 10 mL of water for a final concentration of RAL 10 mg/mL. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension.
- **Do not shake the oral suspension.** Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document. For neonates, most of the prepared oral suspension will be discarded, as the volume for the required dose is much smaller than 10 mL.

## Metabolism/Elimination

- UGT1A1-mediated glucuronidation

## Raltegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving RAL twice daily.
- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving either RAL 1,200 mg once daily or RAL 400 mg twice daily.
- No studies have been conducted on the use of RAL HD in patients with hepatic impairment. Therefore, administering RAL HD **is not recommended** in patients with hepatic impairment.
- The effect of severe hepatic impairment on RAL pharmacokinetics has not been studied.

## Raltegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with any degree of renal impairment.

<sup>b</sup> The RAL 100-mg chewable tablet can be divided into equal halves.

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

- **Metabolism:** The major route of raltegravir (RAL) elimination is mediated through glucuronidation by uridine diphosphate glucuronyl transferase (UGT1A1).
- Coadministering RAL with inducers of UGT1A1, such as rifampin and tipranavir, may result in reduced plasma concentrations of RAL. Inhibitors of UGT1A1, such as atazanavir, may increase plasma concentrations of RAL. No dosing modifications are recommended when RAL is coadministered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r). However, RAL high-dose (HD) tablets **should not be coadministered** with TPV/r.
- In adults, an increased dose of RAL is recommended when it is coadministered with rifampin. For adults receiving rifampin, the recommended RAL dose is 800 mg twice daily. **Do not coadminister** rifampin with once-daily RAL HD tablets. In children aged **4 weeks to <12 years** who had tuberculosis (TB)/HIV coinfection and who were taking rifampin, RAL 12 mg/kg per dose twice daily of the chewable tablet formulation safely achieved pharmacokinetic (PK) targets.<sup>1,2</sup>
- Aluminum-containing antacids and magnesium-containing antacids may reduce RAL plasma concentrations and **should not be coadministered** with RAL.
- Significant drug interactions may be more likely to occur with RAL HD once daily.  $C_{\text{trough}}$  concentrations in adults are approximately 30% lower with RAL HD 1,200 mg once daily than with RAL 400 mg twice daily. A lower  $C_{\text{trough}}$  increases the potential for clinically significant drug interactions with interfering drugs that decrease RAL exposure and further lower  $C_{\text{trough}}$ . In addition to aluminum-containing and magnesium-containing antacids, the following drugs **should not be coadministered** with the RAL HD formulation: calcium carbonate, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug-metabolizing enzymes on RAL is unknown; coadministration with phenytoin, phenobarbital, and carbamazepine **is not recommended**.
- Before administering RAL, clinicians should carefully review a patient's medication profile for potential drug interactions with RAL.

**Major Toxicities**

- **More common:** Nausea, headache, dizziness, diarrhea, fatigue, itching, insomnia.
- **Less common:** Abdominal pain, vomiting. Patients with chronic active hepatitis B virus infection and/or hepatitis C virus infection are more likely to experience a worsening adverse events (AEs) grade from baseline for laboratory abnormalities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than patients who are not coinfecting.
- **Rare:** Moderate to severe increase in creatine phosphokinase levels. Use RAL with caution in patients who are receiving medications that are associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with a history of these conditions. Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis. Thrombocytopenia. Cerebellar ataxia. Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications.

## **Resistance**

The International AIDS Society-USA (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*

RAL 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  $\geq 2$  kg. The current pediatric FDA approval and dose recommendations are based on evaluations of 122 patients aged  $\geq 4$  weeks to 18 years who participated in IMPAACT P1066 and 42 full-term neonates who were treated for  $\leq 6$  weeks starting from birth and followed for a total of 24 weeks during IMPAACT P1110.<sup>3</sup>

The FDA has approved RAL HD, which allows for once-daily dosing, for use in children and adolescents weighing  $\geq 40$  kg.

### *Efficacy in Clinical Trials*

RAL has been evaluated in adults in three large, randomized clinical trials: STARTMRK, SPRING-2, and ACTG A5257. STARTMRK compared the safety and efficacy of a RAL-containing regimen and an efavirenz (EFV)-containing regimen. At 48 weeks, RAL was noninferior to EFV. However, more patients discontinued EFV during the longer follow-up periods of 4 and 5 years, and RAL was found to be virologically and immunologically superior to EFV.<sup>4-6</sup> Results from the SPRING-2 study in treatment-naive adults showed that RAL and dolutegravir (DTG) were equally effective and had similar safety profiles.<sup>7</sup> ACTG A5257 compared RAL to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but RAL had better tolerability.<sup>8</sup>

RAL was studied in infants, children, and adolescents in IMPAACT P1066, an open-label trial that evaluated PKs, safety, tolerability, and efficacy. In 96 participants aged 2 to 18 years who were mostly antiretroviral therapy (ART)-experienced, 79.1% of the patients achieved a favorable viral load response (i.e., viral loads  $< 400$  copies/mL or  $\geq 1$  log<sub>10</sub> decline in viral load) while receiving the currently recommended dose of RAL. Infants and toddlers aged  $\geq 4$  weeks to  $< 2$  years were also enrolled in IMPAACT P1066 and received treatment with RAL oral suspension. At Weeks 24 and 48, 61% of the participants (14 of 23 infants and toddlers) had HIV viral loads  $< 400$  copies/mL.<sup>9-11</sup> FDA approval for the use of RAL in infants as young as 4 weeks of age was based on the results of this study.

The ONCEMRK study compared RAL 1,200 mg once daily (taken as two 600-mg RAL HD tablets) to RAL 400 mg twice daily in treatment-naive adults. Once-daily dosing of RAL using the HD tablets was approved by the FDA for adults and children weighing  $\geq 40$  kg who are either treatment-naive or virologically suppressed on a twice-daily RAL regimen.

### ***Efficacy and Pharmacokinetics of Once-Daily Dosing in Children and Adults***

RAL PKs exhibit considerable intrasubject and intersubject variability.<sup>12,13</sup> Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naive patients with HIV were randomized to receive RAL 800 mg once daily or RAL 400 mg twice daily. After 48 weeks of treatment, the 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<sub>trough</sub> concentrations below 45 nM (20 ng/mL) were at the greatest risk of experiencing treatment failure.<sup>12,13</sup> Overall drug exposures were similar in both groups, but the association between higher risk of treatment failure and lower C<sub>trough</sub> concentrations suggests that maintaining RAL trough plasma concentrations above 45 nM (20 ng/mL) is important for efficacy.<sup>12,13</sup>

Once-daily dosing with RAL 1,200 mg was found to be as effective as dosing with RAL 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either RAL 1,200 mg once daily (taken as two 600-mg tablets) or RAL 400 mg twice daily plus tenofovir disoproxil fumarate plus

emtricitabine. After 48 weeks, 89% of participants on the once-daily dose and 88% of participants on the twice-daily dose reached viral loads of <40 copies. There was no difference in discontinuation rates due to AEs between the two groups.<sup>14</sup> In May 2017, once-daily dosing of RAL using the HD tablets was approved by the FDA for adults and children weighing  $\geq 40$  kg who are either treatment-naïve or virologically suppressed on a twice-daily RAL regimen. The use of once-daily dosing with the HD tablets has not been studied in pediatric patients. Population PK modeling and simulations of once-daily dosing with RAL HD tablets predict that this dosing schedule will produce drug exposures that are similar to those observed in adult patients during ONCEMRK.<sup>3,15</sup>

Dosing with three 400-mg RAL tablets once daily and dosing with two 600-mg RAL HD tablets once daily are expected to produce similar PK profiles. In adults enrolled in ONCEMRK, the  $C_{\text{trough}}$  concentrations were approximately 30% lower in participants taking once-daily RAL HD tablets than in those taking RAL 400 mg twice daily. Because of this, there is a greater potential for significant drug interactions with once-daily dosing of RAL; coadministering once-daily RAL with drugs that decrease drug exposure may further decrease  $C_{\text{trough}}$ .  $C_{\text{max}}$  is approximately six times higher in patients receiving RAL 1,200 mg once daily than in those receiving RAL 400 mg twice daily, with a two-fold higher area under the curve (AUC).

While modeling and simulations for pediatric patients indicate that PK targets are met using the once-daily RAL 1,200 mg dose, there are no clinical data on the use of this dose in 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. Dose-related central nervous system toxicities, such as insomnia or hyperactivity, may occur in children who are exposed to very high concentrations of RAL.<sup>3</sup>

### ***Efficacy and Pharmacokinetics in Children***

IMPAACT P1066 evaluated the PKs, safety, and efficacy of RAL 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.<sup>10,11</sup>

**Table A. Summary of IMPAACT P1066 Pharmacokinetic Results by Cohort**

Age	Cohort	RAL Formulation	Number of Participants with Intensive PK Data	Mean Dose of RAL (mg/kg)	GM AUC <sub>0-12h</sub> $\mu\text{M}\cdot\text{h}$ (CV%) <sup>a</sup>	GM C <sub>12h</sub> nM (CV%) <sup>b</sup>
12 Years to <19 Years	I	Film-coated tablet	11	9.3	15.7 (98%)	333 (78%)
6 Years to <12 Years	IIA	Film-coated tablet	11	13.5	15.8 (120%)	246 (221%)
6 Years to <12 Years	IIB	Chewable tablet	10	6.5	22.6 (34%)	130 (88%)
2 Years to <6 Years	III	Chewable tablet	12	6.2	18.0 (59%)	71 (55%)
6 Months to <2 Years	IV	Oral suspension	8	5.9	19.8 (34%)	108 (52%)
4 Weeks to <6 Months	V	Oral suspension	11	5.7	22.3 (40%)	117 (68%)

<sup>a</sup> PK targets for Cohorts I–III: AUC<sub>0-12h</sub> 14–25  $\mu\text{M}\cdot\text{h}$  (6–11 mg·h/L); C<sub>12h</sub> nM  $\geq 33$  nM (14.7 ng/mL)

<sup>b</sup> PK targets for Cohorts IV–V: AUC<sub>0-12h</sub> 14–45  $\mu\text{M}\cdot\text{h}$  (6–20 mg·h/L); C<sub>12h</sub> nM  $\geq 75$  nM (33.3 ng/mL)

**Key:** AUC = area under the curve; C<sub>12h</sub> = concentration at 12 hours (trough); CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic; RAL = raltegravir

### ***Children Aged 2 Years to 18 Years***

IMPAACT P1066 was a Phase 1/2 open-label multicenter study that evaluated the PK profile, safety, tolerability, and efficacy of various formulations of RAL in ART-experienced children and adolescents with HIV aged 2 to 18 years. RAL was administered in combination with an optimized background ARV regimen.<sup>11,16</sup> Subjects received either the RAL 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing  $\geq 25$  kg) or the chewable tablet formulation at a dose of RAL 6 mg/kg twice

daily (patients aged 2 years to <12 years). In IMPAACT P1066, the initial dose-finding stage included an intensive PK evaluation in various age cohorts (Cohort 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 that were similar to those seen in adults: PK targets were a geometric mean (GM)  $AUC_{0-12h}$  of  $14 \mu M \cdot h$  to  $25 \mu M \cdot h$  and a GM 12-hour concentration ( $C_{12h}$ )  $>33$  nM. Additional participants were then enrolled in each age cohort to evaluate the long-term efficacy, tolerability, and safety of RAL.

A total of 126 treatment-experienced participants were enrolled, with 96 participants receiving the final recommended dose of RAL. Only treatment-experienced patients were eligible to enroll, and the optimized regimen was determined by the site investigators. Adolescents tended to be more treatment-experienced and have more advanced disease than those in the younger cohorts, with 75% having Centers for Disease Control and Prevention 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%).<sup>11</sup> 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 RAL-associated mutations were detected in 12 out of 34 of those patients. The frequency, type, and severity of AEs through Week 48 were comparable to those observed in adult studies. AEs were commonly reported, but few serious AEs were considered to be drug-related. Patients with AEs that were considered to be drug-related included one patient with Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia, 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.<sup>11</sup> Overall, RAL 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.<sup>17</sup>

Among 19 children and adolescents who were nonresponders with multidrug-resistant virus in the HIV Spanish Cohort (CoRISe), all had good virologic response and improved CD4 counts when RAL was included in an optimized regimen.<sup>9</sup> Experience from the French expanded access program in treatment-experienced adolescents supports the good virologic and immunologic results observed in IMPAACT P1066.<sup>18,19</sup> Overall virologic and immunologic outcomes have been good among additional cohorts of treatment-experienced children and adolescents from low-income and middle-income countries.<sup>20,21</sup>

### ***Children Aged $\geq 4$ Weeks to $< 2$ Years***

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to  $< 2$  years who were administered the granules for RAL oral suspension in combination with an optimized background 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  $14 \mu M \cdot h$  to  $45 \mu M \cdot h$  and a GM  $C_{12h} \geq 75$  nM (33.3 ng/mL). These targets were modified so that an estimated  $>90\%$  of patients would have  $C_{12h}$  above the 45 nM threshold. By Week 48, two subjects experienced AEs that were thought to be related to the study drug: one patient experienced a serious erythematous rash that resulted in permanent discontinuation of RAL, and one patient experienced immune reconstitution inflammatory syndrome. Virologic success, defined as  $\geq 1 \log_{10}$  decline in HIV RNA or  $<400$  copies/mL at 48 weeks, was achieved in  $>87\%$  of participants. At 48 weeks of follow up, 45.5% of subjects had HIV RNA  $<50$  copies/mL and mean CD4 count increases of 527.6 cells/ $mm^3$  (7.3%). There were four subjects in Cohort IV who experienced virologic failure by Week 48 and one subject with a RAL-associated resistance mutation. Overall, the granules for oral suspension, at a dose of approximately RAL 6 mg/kg twice daily, were well tolerated and had good efficacy.<sup>10</sup>

### ***Long-Term Follow Up in Children***

The IMPAACT P1066 study team reported results regarding the safety and efficacy of different RAL formulations at 240 weeks in children enrolled in this multicenter trial.<sup>22</sup> Eligible participants were children

aged 4 weeks to 18 years who had previously been treated with ART and who were experiencing virologic failure at the time of enrollment. RAL was added to an optimized ARV regimen in all participants. RAL was well tolerated, and there were few serious clinical or laboratory safety events noted during the study.<sup>22</sup>

The proportion of participants who achieved virologic success at 240 weeks varied by the RAL formulation used: 19 of 43 children (44.2%) who received RAL 400-mg tablets; 24 of 31 children (77.4%) who received chewable tablets; and 13 of 15 children (86.7%) who received the oral granules for suspension. RAL resistance was documented in 19 of 50 patients (38%) who experienced virologic rebound after initial suppression. These results suggest that younger children with less treatment experience are more likely to have sustained virologic suppression, while older children with an extensive treatment history are more likely to experience treatment failure and develop resistance to RAL. Poor adherence among adolescents may have contributed to the lower efficacy observed in older children who received the RAL 400-mg tablets.<sup>22</sup> In the accompanying commentary, the authors conclude that these findings support the use of RAL in infants and young children, who have few treatment options.<sup>23</sup> However, in older children and adolescents, INSTIs such as DTG (which has a higher genetic barrier to resistance than RAL) are preferred.<sup>23</sup>

### *Neonates Aged <4 Weeks*

RAL is metabolized by UGT1A1, the same enzyme that is responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. Washout PKs of RAL in neonates born to pregnant women with HIV was studied in IMPAACT P1097.<sup>24</sup> The neonatal plasma half-life of RAL was highly variable, ranging from 9.3 to 184 hours. This suggests that neonatal development may impact UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of RAL. **RAL competes with unconjugated bilirubin for albumin binding sites. When RAL plasma concentrations are extremely high, unconjugated bilirubin may be displaced from albumin by RAL and cross the blood-brain barrier, leading to bilirubin-induced neurologic dysfunction. The effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant unless concentrations that are 50-fold to 100-fold higher than typical peak concentrations are reached (approximately 5,000 ng/mL).**<sup>25</sup>

IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates with or without *in utero* RAL exposure who were exposed to HIV and who are at risk of acquiring HIV. RAL-exposed neonates were those whose mothers received RAL within 2 to 24 hours of delivery. For RAL-exposed neonates, the initial dose of RAL was delayed until 12 to 60 hours after delivery. The study design included two cohorts: Cohort 1 infants received two RAL doses that were administered 1 week apart, and Cohort 2 infants received daily RAL doses for the first 6 weeks of life. PK data from Cohort 1 and from older infants and children were combined in a population PK model, and simulations were used to select the following RAL dosing regimen for evaluation in infants in Cohort 2: RAL 1.5 mg/kg daily, starting within 48 hours of life and continuing through Day 7; RAL 3 mg/kg twice daily on Days 8 to 28 of life; and RAL 6 mg/kg twice daily after 4 weeks of age.<sup>26</sup> Protocol exposure targets for each subject were AUC<sub>0-24hr</sub> 12 mg·h/L to 40 mg·h/L, AUC<sub>0-12hr</sub> 6 mg·h/L to 20 mg·h/L, and C<sub>12h</sub> or C<sub>24h</sub> >33 ng/mL. Safety was assessed using clinical and laboratory evaluations.<sup>24,27,28</sup>

Twenty-six RAL-naïve infants and 10 RAL-exposed infants were enrolled in Cohort 2; 25 RAL-naïve infants and 10 RAL-exposed infants had evaluable PK results and safety data. Results for the RAL-naïve infants and RAL-exposed infants who were enrolled in Cohort 2 are contained in the summary table below.<sup>28</sup>

**Table B. Raltegravir Pharmacokinetic Parameters for Raltegravir-Naive and Raltegravir-Exposed Neonates**

PK Parameter	Initial Dose: RAL 1.5 mg/kg Once Daily RAL-Naive (n = 25) <sup>d</sup>		Initial Dose: RAL 1.5 mg/kg Once Daily RAL-Exposed (n = 10)		Days 15–18: RAL 3.0 mg/kg Twice Daily RAL-Naive (n = 24) <sup>e</sup>		Days 15–18: RAL 3.0 mg/kg Twice Daily RAL-Exposed (n = 10) <sup>f</sup>	
	GM (CV%)	Target	GM (CV%)	Target	GM (CV%)	Target	GM (CV%)	Target
AUC <sub>0-24h</sub> (mg·h/L) <sup>a</sup>	38.2 (42.0%)	Met: 13 Above: 11 Below: 0	42.9 (25.3%)	Met: 4 Above: 6 Below: 0	-----	-----	-----	-----
AUC <sub>0-12h</sub> (mg·h/L)	-----	-----	-----	-----	14.3 (49.5%)	Met: 14 Above: 8 Below: 1	18.3 (62.8%)	Met: 3 Above: 5 Below: 1
C <sub>trough</sub> (ng/mL) <sup>b</sup>	948 (84.0%)	Met: 25 Below: 0	946 (74.0%)	Met: 10 Below: 0	176 (162.1%)	Met: 22 Below: 2	274 (176.4%)	Met: 8 Below: 2
C <sub>max</sub> (ng/mL) <sup>c</sup>	2,350 (36.5%)	Met: 25 Above: 0	2,565 (23.1%)	Met: 10 Above: 0	2,849 (47.5%)	Met: 24 Above: 0	3,667 (46.3%)	Met: 9 Above: 0
T <sub>max</sub> (hours)	5.4 (71.5%)	N/A	3.8 (88.8%)	N/A	2.3 (77.1%)	N/A	1.9 (52.3%)	N/A
T <sub>1/2</sub> (hours)	15.8 (101.4%)	N/A	14.4 (69.5%)	N/A	2.5 (34.1%)	N/A	2.9 (20.7%)	N/A

<sup>a</sup> AUC targets: AUC<sub>0-24h</sub> 12–40 mg·h/L and AUC<sub>0-12h</sub> 6–20 mg·h/L.

<sup>b</sup> C<sub>trough</sub> concentration >33 ng/mL. For initial dose, C<sub>last</sub> collected at 24 hours was used. For Days 15 to 18, C<sub>12h</sub> was estimated when the 12 hours post-dose sample was collected earlier than 12 hours after dosing (the protocol specified a sample collection time of 8 to 12 hours post dose).

<sup>c</sup> C<sub>max</sub> <8,724 ng/mL.

<sup>d</sup> AUC<sub>0-24h</sub> could not be estimated for one infant.

<sup>e</sup> AUC<sub>0-12h</sub> could not be estimated for one infant with delayed absorption.

<sup>f</sup> AUC<sub>0-12h</sub> and C<sub>max</sub> could not be estimated for one infant with incomplete sample collection.

**Key:** AUC = area under the curve; C<sub>last</sub> = last measurable plasma concentration; C<sub>max</sub> = maximum concentration; C<sub>trough</sub> = trough concentration; CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic; RAL = raltegravir; T<sub>1/2</sub> = half-life; T<sub>max</sub> = time to reach maximum concentration

Daily RAL was safe and well tolerated during the first 6 weeks of life. Infants were treated for up to 6 weeks from birth and followed for a total of 24 weeks. All GM protocol exposure targets were met. In some infants, AUC<sub>0-24h</sub> following the initial dose was slightly above the target range, but this is considered acceptable given the rapid increase in RAL metabolism during the first week of life. The PK targets and the safety guidelines were met for both RAL-naive and RAL-exposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory AEs were reported among the RAL-naive infants: Grade 4 transient neutropenia occurred in one infant who received a zidovudine-containing regimen; two bilirubin elevations (one Grade 1 and one Grade 2) were considered nonserious and did not require specific therapy.<sup>3</sup> Among the RAL-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 RAL 2 to 24 hours prior to delivery should have their first dose of RAL delayed until 24 to 48 hours after birth.<sup>27,28</sup> RAL can be safely administered to full-term infants using the daily dosing regimen that was studied in P1110. This regimen **is not recommended** for use in preterm infants.

Dosing in preterm infants has not been well studied. Two case reports of preterm infants who received RAL to prevent perinatal transmission have been published.<sup>29,30</sup> These case reports involved one infant born at a gestational age of 24 weeks and 6 days who weighed 800 g and another infant born at 33 weeks gestation who weighed 1,910 g. In both infants, intermittent dosing of RAL was done using real-time therapeutic drug monitoring in the neonatal intensive care unit.<sup>29,30</sup> Less frequent dosing was required because RAL elimination was significantly delayed in these preterm infants. **RAL PKs and safety must be studied in preterm infants before RAL can be safely used without real-time PK monitoring in this population.**

### Formulations

The PKs of RAL in adult patients with HIV who swallowed intact 400-mg tablets were compared 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.<sup>31</sup> In adult volunteers, the PKs of RAL 800 mg taken once daily by chewing was compared to the PKs of two doses of RAL 400 mg taken every 12 hours by swallowing. Participants who took RAL by chewing had significantly higher drug exposure and reduced PK variability than those who swallowed whole tablets according to current recommendations.<sup>32</sup> According to the manufacturer, the film-coated tablets must be swallowed whole.

The RAL chewable tablet and oral suspension have higher oral bioavailability than the 400-mg, film-coated tablet, according to a comparative study in healthy adult volunteers.<sup>33</sup> Compared with the RAL 400-mg tablet formulation, the RAL 600-mg tablet has higher relative bioavailability.<sup>3,34</sup> Interpatient and inpatient variability for PK parameters of RAL are considerable, especially with the film-coated tablets.<sup>3,35</sup> Because of differences in the bioavailability of various formulations, the dosing recommendations for each formulation differ, and the formulations **are not interchangeable**. When prescribing RAL, clinicians should refer to the appropriate dosing table for the chosen formulation. While the RAL 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.<sup>36</sup> An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including **water, apple juice, and breast milk. The use of RAL chewable tablets as dispersible tablets in children aged <2 years has been studied in IMPAACT P1101 for infants and toddlers with TB/HIV coinfection who received rifampin as part of their TB treatment. The use of RAL chewable tablets dispersed in water at a dose of RAL 12 mg/kg per dose twice daily safely achieved PK targets.**<sup>1,2</sup>

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.<sup>10,11</sup> **The acceptability and feasibility of administering RAL granules for oral suspension in a low-resource setting has been studied in a clinic in South Africa. With proper training by health care personnel, caregivers were able to prepare the suspension safely and accurately.**<sup>37</sup>

## References

1. Meyers T, Samson P, Acosta EP, et al. Pharmacokinetics and safety of a raltegravir-containing regimen in HIV-infected children aged 2-12 years on rifampicin for tuberculosis. *AIDS*. 2019;33(14):2197-2203. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31689263>.
2. Krogstad P, Samson P, Acosta E, et al. Pharmacokinetics of raltegravir in HIV/TB cotreated infants and young children. Presented at: Conference on Retroviruses and Opportunistic Infections. 2020. Boston, Massachusetts.
3. Raltegravir [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/022145s038,205786s007,0203045s0151bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022145s038,205786s007,0203045s0151bl.pdf)
4. Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19647866>.

5. DeJesus E, Rockstroh JK, Lennox JL, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. *HIV Clin Trials*. 2012;13(4):228-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22849964>.
6. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013;63(1):77-85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23412015>.
7. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013;13(11):927-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24074642>.
8. Lennox JL, Landovitz RJ, Ribaldo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161(7):461-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25285539>.
9. Briz V, Leon-Leal JA, Palladino C, et al. Potent and sustained antiviral response of raltegravir-based highly active antiretroviral therapy in HIV type 1-infected children and adolescents. *Pediatr Infect Dis J*. 2012;31(3):273-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22330165>.
10. Nachman S, Alvero C, Acosta EP, et al. Pharmacokinetics and 48-week safety and efficacy of raltegravir for oral suspension in human immunodeficiency virus type-1-infected children 4 weeks to 2 years of age. *J Pediatric Infect Dis Soc*. 2015;4(4):e76-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26582887>.
11. Nachman S, Zheng N, Acosta EP, et al. Pharmacokinetics, safety, and 48-week efficacy of oral raltegravir in HIV-1-infected children aged 2 through 18 years. *Clin Infect Dis*. 2014;58(3):413-422. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24145879>.
12. Rizk ML, Hang Y, Luo WL, et al. Pharmacokinetics and pharmacodynamics of once-daily versus twice-daily raltegravir in treatment-naive HIV-infected patients. *Antimicrob Agents Chemother*. 2012;56(6):3101-3106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22430964>.
13. Rizk ML, Du L, Bennetto-Hood C, et al. Population pharmacokinetic analysis of raltegravir pediatric formulations in HIV-infected children 4 weeks to 18 years of age. *J Clin Pharmacol*. 2015;55(7):748-756. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25753401>.
14. Cahn P, Sax PE, Squires K, et al. Raltegravir 1200 mg once daily vs 400 mg twice daily, with emtricitabine and tenofovir disoproxil fumarate, for previously untreated HIV-1 infection: week 96 results from ONCEMRK, a randomized, double-blind, noninferiority trial. *J Acquir Immune Defic Syndr*. 2018;78(5):589-598. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29771789>.
15. Food and Drug Administration. Raltegravir Clinical Pharmacology Review. 2017. Available at: <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM562849.pdf>.
16. Larson KB, King JR, Acosta EP. Raltegravir for HIV-1 infected children and adolescents: efficacy, safety, and pharmacokinetics. *Adolesc Health, Med Ther*. 2013;4:79-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24600298>.
17. Tuluc F, Spitsin S, Tustin NB, et al. Decreased PD-1 Expression on CD8 lymphocyte subsets and increase in CD8 tscm cells in children with HIV receiving raltegravir. *AIDS Res Hum Retroviruses*. 2016; 33(2):133-142 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27615375>.
18. Thuret I, Tamalet C, Reliquet V. Raltegravir in children and adolescents: the French expanded access program. Presented at: Conference on Retroviruses and Opportunistic Infections. 2009. Montreal, Canada.
19. Thuret I, Chaix ML, Tamalet C, et al. Raltegravir, etravirine and r-darunavir combination in adolescents with multidrug-resistant virus. *AIDS*. 2009;23(17):2364-2366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19823069>.
20. Nuttall J, Pillay V. Characteristics and early outcomes of children and adolescents treated with darunavir/ritonavir-, raltegravir- or etravirine-containing antiretroviral therapy in the Western Cape Province of South Africa. *S Afr Med J*. 2018;108(2):105-110. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29429441>.
21. Patten G, Puthakanit T, McGowan CC, et al. Raltegravir use in HIV-infected children and adolescents, and outcomes

as a third-line combination antiretroviral therapy (cART) option in the IeDEA consortium. Presented at: International Workshop on HIV Pediatrics. 2018. Amsterdam, Netherlands.

22. Nachman S, Alvero C, Teppler H, et al. Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a Phase 1/2 open label, non-randomised, multicentre trial. *Lancet HIV*. 2018;5(12):e715-e722. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30527329>.
23. Collins IJ, Turkova A. Outcomes in children on raltegravir: a story of two halves. *Lancet HIV*. 2018;5(12):e676-e678. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30527322>.
24. Clarke DF, Acosta EP, Rizk ML, et al. Raltegravir pharmacokinetics in neonates following maternal dosing. *J Acquir Immune Defic Syndr*. 2014;67(3):310-315. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25162819>.
25. Clarke DF, Wong RJ, Wenning L, Stevenson DK, Mirochnick M. Raltegravir in vitro effect on bilirubin binding. *Pediatr Infect Dis J*. 2013;32(9):978-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23470680>.
26. Clarke DF, Mirochnick M, Acosta EP, et al. Use of modeling and simulations to determine raltegravir dosing in neonates: a model for safely and efficiently determining appropriate neonatal dosing regimens: IMPAACT P1110. *J Acquir Immune Defic Syndr*. 2019;82(4):392-398. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31658182>.
27. Lommerse J, Clarke D, Kerbusch T, et al. Maternal-neonatal raltegravir population pharmacokinetics modeling: implications for initial neonatal dosing. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(9):643-653. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31215170>.
28. Clarke DF, Acosta EP, Cababasay M, et al. Raltegravir (RAL) in neonates: Dosing, pharmacokinetics (PK), and safety in HIV-1 exposed neonates at risk of infection (IMPAACT P1110) [published online head of print] *JAIDS*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31913995>.
29. Trahan MJ, Lamarre V, Metras ME, Kakkar F. Use of triple combination antiretroviral therapy with raltegravir as empiric HIV therapy in the high-risk HIV-exposed newborn. *Pediatr Infect Dis J*. 2018; 38(4):410-412. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30153229>.
30. Kreutzwiser D, Sheehan N, Dayneka N, et al. Therapeutic drug monitoring guided raltegravir dosing for prevention of vertical transmission in a premature neonate born to a woman living with perinatally acquired HIV. *Antivir Ther*. 2017;22(6):545-549. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28198351>.
31. Cattaneo D, Baldelli S, Cerea M, et al. Comparison of the in vivo pharmacokinetics and in vitro dissolution of raltegravir in HIV patients receiving the drug by swallowing or by chewing. *Antimicrob Agents Chemother*. 2012;56(12):6132-6136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22964253>.
32. Cattaneo D, Cossu MV, Fucile S, et al. Comparison of the pharmacokinetics of raltegravir given at 2 doses of 400 mg by swallowing versus one dose of 800 mg by chewing in healthy volunteers: a randomized, open-label, 2-period, single-dose, crossover Phase 1 study. *Ther Drug Monit*. 2015;37(1):119-125. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24988438>.
33. Brainard D, Gendrano N, Jin B, et al. A pharmacokinetic comparison of adult and pediatric formulations of RAL in healthy adults. Presented at: Conference on Retroviruses and Opportunistic Infections. 2010. San Francisco, California.
34. Krishna R, Rizk ML, Larson P, Schulz V, Kesisoglou F, Pop R. Single- and multiple-dose pharmacokinetics of once-daily formulations of raltegravir. *Clin Pharmacol Drug Dev*. 2018;7(2):196-206. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28419778>.
35. Siccardi M, D'Avolio A, Rodriguez-Novoa S, et al. Inpatient and outpatient pharmacokinetic variability of raltegravir in the clinical setting. *Ther Drug Monit*. 2012;34(2):232-235. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22406652>.
36. Teppler H, Thompson K, Chain A, Mathe M, Nachman S, Clarke D. Crushing of raltegravir (RAL) chewable tablets for administration in infants and young children. International Workshop on HIV Pediatrics. 2017. Paris, France.
37. Archary M, Zaroni BC, Lallemand M, Suwannaprom P, Clarke D, Penazzato M. Acceptability and feasibility of using raltegravir oral granules for suspension for the treatment of neonates in a low resource setting. *Pediatr Infect Dis J*. 2020;39(1):57-60. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31815839>.

## Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

# Cobicistat (COBI, Tybost) (Last updated April 14, 2020; last reviewed April 14, 2020)

## 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 10 mg
- [Prezcobix] Darunavir 800 mg/cobicistat 150 mg
- [Stribild] Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

## Dosing Recommendations

### Cobicistat is a Pharmacokinetic Enhancer:

- The only use of cobicistat (COBI) is as a pharmacokinetic (PK) enhancer (boosting agent) for certain protease inhibitors (PIs) and integrase strand transfer inhibitors. COBI **is not interchangeable** with ritonavir (RTV).

### Child and Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- COBI 150 mg with atazanavir (ATV) 300 mg administered at the same time and with food

### Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose:

- COBI 150 mg with darunavir (DRV) 800 mg administered at the same time and with food

### [Evotaz] Atazanavir/Cobicistat

#### Child and Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily with food
- Use in combination with other ARV drugs.

### [Genvoya] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (TAF)

#### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose:

- One tablet once daily with food

### [Prezcobix] Darunavir/Cobicistat

#### Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose:

- One tablet once daily with food

## Selected Adverse Events

- COBI is an inhibitor of renal tubular transporters of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate, with no change in glomerular function.

## Special Instructions

- COBI 150 mg **is not interchangeable** with RTV, but it has a PK boosting effect that is comparable to RTV 100 mg.
- Drug interactions may differ between RTV and COBI, because COBI is a stronger P-glycoprotein inhibitor and lacks some of the induction effects of RTV.
- **Do not administer** COBI with RTV or with FDC tablets that contain COBI.
- COBI **is not recommended** for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir used in combination with a PI).
- Using COBI with PIs other than once-daily ATV 300 mg or DRV 800 mg **is not recommended**.
- Patients with a confirmed increase in serum creatinine  $>0.4$  mg/dL from baseline should be closely monitored for renal safety.
- When using COBI in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while the patient is receiving therapy (see [Table 15i](#)). In patients who are at risk of

- Use in combination with other ARV drugs.

**[Stribild] Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (TDF)**

*Child and Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily with food
- The Panel recommends using Stribild only in patients with sexual maturity ratings of 4 or 5.

**[Symtuza] Darunavir/Cobicistat/Emtricitabine/TAF**  
*Child and Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet once daily with food

renal impairment, serum phosphate should also be monitored.

- For information on crushing and cutting tablets, please see [this table](#) from Toronto General Hospital.

### Metabolism/Elimination

- COBI is a strong inhibitor of cytochrome P450 (CYP) 3A4 and a weak inhibitor of CYP2D6.

### Cobicistat Dosing in Patients with Hepatic Impairment:

- COBI does not require dose adjustment in patients with mild to moderate hepatic impairment. No data are available in patients with severe hepatic impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.<sup>1</sup>
- Stribild, Genvoya, and Symtuza **should not be used** in patients with severe hepatic impairment.<sup>1</sup>

### Cobicistat Dosing in Patients with Renal Impairment:

- COBI does not require a dose adjustment in patients with renal impairment, including those with severe renal impairment. Dosing recommendations for medications that are coadministered with COBI should be followed.<sup>1</sup>
- The use of COBI plus TDF **is not recommended** in patients with creatinine clearance (CrCl)  $< 70$  mL/min. Dose adjustments for TDF are required for patients with CrCl  $< 50$  mL/min, and the necessary dose adjustments for TDF when this drug is used with COBI have not been established in this group of patients.<sup>1</sup>
- 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. 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.

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

- *Metabolism:* Metabolism of cobicistat (COBI) is mainly via cytochrome P450 (CYP) 3A4 and, to a lesser degree, CYP2D6. COBI is a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. COBI

also inhibits the breast cancer resistance protein, P-glycoprotein (P-gp), the organic anion transporting polypeptides OATP1B1 and OATP1B3, and multidrug and toxin extrusion 1 (MATE1). Unlike ritonavir (RTV), COBI does not demonstrate any enzyme-inducing effects. The potential exists for multiple drug interactions when using COBI. Before COBI is administered, a patient's medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs.

- *Nucleoside reverse transcriptase inhibitors:* COBI is a strong P-gp inhibitor; thus, a dose of tenofovir alafenamide (TAF) 10 mg combined with COBI produces tenofovir (TFV) exposures that are similar to those produced by TAF 25 mg without COBI.<sup>2</sup> **COBI increases plasma TFV exposures by 23% when it is coadministered with TDF; thus, renal safety should be monitored in patients who are receiving this combination.**<sup>1,3</sup>
- *Non-nucleoside reverse transcriptase inhibitors:* Efavirenz, etravirine, and nevirapine **should not be used** with COBI.
- *Protease inhibitors:* Using COBI as a dual booster for elvitegravir (EVG) and darunavir (DRV) has been studied in people with HIV and people without HIV, and the evidence is conflicting. When EVG plus COBI plus DRV was administered to people without HIV, the C<sub>trough</sub> concentration of EVG was 50% lower than the C<sub>trough</sub> concentration seen in people who received elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/c/FTC/TDF) without DRV.<sup>4</sup> When EVG/c/FTC/TAF was administered with DRV to patients with HIV, both DRV and EVG concentrations were comparable to those seen in historic controls.<sup>5</sup>
- *Integrase inhibitors:* In one small study, dolutegravir (DTG) C<sub>trough</sub> concentrations were 107% higher when DTG was administered with darunavir/cobicistat (DRV/c) than when it was administered with darunavir/ritonavir.<sup>6</sup> Bictegravir (BIC) area under the curve increases 74% when BIC is administered with DRV/c.<sup>7</sup>
- *Corticosteroids:* Increased serum concentrations of corticosteroids can occur when corticosteroids and COBI are coadministered; this can lead to clinically significant adrenal suppression. Adrenal suppression occurs regardless of whether the corticosteroids are administered orally or by some other route (e.g., intranasal, inhaled, interlaminar, intraarticular) and regardless of whether the corticosteroids are administered routinely or intermittently. A possible exception is beclomethasone, which appears to be a relatively safe option with inhaled or intranasal administration.<sup>8,9</sup>

### **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. COBI has no antiviral activity. Its sole use is as a pharmacokinetic enhancer of antiretroviral drugs.

### **Pediatric Use**

#### *Approval*

COBI, as a component of Stribild, is approved by the Food and Drug Administration (FDA) at the adult dose for use in children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends limiting the use of Stribild to those with a sexual maturity rating of 4 or 5. COBI, as a component of Genvoya, is approved by the FDA at the adult dose for use in children weighing  $\geq 25$  kg. **COBI alone (as Tybost) is approved by the FDA at the adult dose for use in children weighing  $\geq 35$  kg when used in combination with ATV, and in children weighing  $\geq 40$  kg when used in combination with DRV.** The FDA has not approved the use of COBI

coformulated with ATV (as Evotaz) or DRV (as Prezcofix), or COBI as a component of Symtuza, in children aged <18 years. However, the Panel considers these fixed-dose combinations appropriate for pediatric use, given that the individual component drugs have been approved for use in children and adolescents who meet certain weight-based indications.

## References

1. Tybost [package insert]. Food and Drug Administration. 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/203094s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203094s014lbl.pdf)
2. Ramanathan S, Wei X, Custudio J, et al. Pharmacokinetics of a novel EVG/COBI/FTC/GS-7340 single tablet regimen. Abstract O-13. Presented at: International Workshop on Clinical Pharmacology of HIV Therapy. 2012. Barcelona, Spain. Available at: [http://www.natap.org/2012/pharm/Pharm\\_24.htm](http://www.natap.org/2012/pharm/Pharm_24.htm).
3. Custodio J, Garner W, Jin F, et al. Evaluation of the drug interaction potential between the pharmacokinetic enhancer and tenofovir disoproxil fumarate in healthy subjects. Presented at: International Workshop on Clinical Pharmacology of HIV Therapy. 2013. Amsterdam, Netherlands.
4. Ramanathan S, Wang H, Szwarcberg J, Kearney BP. Safety/tolerability, pharmacokinetics, and boosting of twice-daily cobicistat administered alone or in combination with darunavir or tipranavir. Abstract P-08. Presented at: International Workshop on Clinical Pharmacology of HIV Therapy. 2012. Barcelona, Spain. Available at: [http://www.natap.org/2012/pharm/Pharm\\_28.htm](http://www.natap.org/2012/pharm/Pharm_28.htm).
5. Gutierrez-Valencia A, Trujillo-Rodriguez M, Fernandez-Magdaleno T, Espinosa N, Viciano P, Lopez-Cortes LF. Darunavir/cobicistat showing similar effectiveness as darunavir/ritonavir monotherapy despite lower trough concentrations. *J Int AIDS Soc*. 2018;21(2). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29430854>.
6. Gervasoni C, Riva A, Cozzi V, et al. Effects of ritonavir and cobicistat on dolutegravir exposure: when the booster can make the difference. *J Antimicrob Chemother*. 2017;72(6):1842-1844. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28333266>.
7. Zhang H, Custudio J, Wei X, et al. Clinical Pharmacology of the HIV integrase strand transfer inhibitor bictegravir. Abstract 40. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, Washington. Available at: <http://www.croiconference.org/sessions/clinical-pharmacology-hiv-integrase-strand-transfer-inhibitor-bictegravir>.
8. Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV Med*. 2013;14(9):519-529. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23590676>.
9. Boyd SD, Hadigan C, McManus M, et al. Influence of low-dose ritonavir with and without darunavir on the pharmacokinetics and pharmacodynamics of inhaled beclomethasone. *J Acquir Immune Defic Syndr*. 2013;63(3):355-361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23535292>.

## Ritonavir (RTV, Norvir) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

**Oral Powder:** 100 mg per packet

**Oral Solution:** 80 mg/mL. Oral solution contains 43% (v/v) ethanol and approximately 27% (w/v) propylene glycol.

**Tablets:** 100 mg

#### Generic Formulation

- 100 mg tablets

#### Fixed-Dose Combination Solution:

- [Kaletra] Lopinavir 80 mg/ritonavir 20 mg/mL. Oral solution contains 42.4% (v/v) ethanol and 15.3% (w/v) propylene glycol.

#### Fixed-Dose Combination Tablets:

- [Kaletra] Lopinavir 100 mg/ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg/ritonavir 50 mg

When using fixed-dose combination (FDC) tablets or solution, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.](#)

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Ritonavir as a Pharmacokinetic Enhancer:

- Ritonavir (RTV) is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of RTV varies and is specific to the drug combination selected. See other sections of the [Drug Appendix](#) for information about the recommended doses of RTV to use with specific PIs. RTV has antiviral activity, but it is not used as an antiviral agent; instead, it is used as a pharmacokinetic enhancer of other PIs.

#### Formulation Considerations:

- The RTV oral solution contains propylene glycol and ethanol.
- The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least RTV 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- RTV oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Hyperglycemia
- Fat maldistribution

### Special Instructions

- Administer RTV with food to increase absorption and reduce the likelihood and severity of GI adverse events.
- **Do not administer** RTV with cobicistat (COBI) or drugs that contain COBI (e.g., Stribild, Genvoya, Prezcoibix, Evotaz).
- **Do not refrigerate** RTV oral solution; store at 68°F to 77°F (20°C to 25°C). Shake the solution well before use.
- RTV 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.

### [Kaletra] Lopinavir/Ritonavir

Infant, Child, Adolescent, and Adult Dose:

- See the [Lopinavir/Ritonavir](#) section of the [Drug Appendix](#).

Administer or discard the mixture within 2 hours of mixing.

#### To Increase Tolerability of Ritonavir Oral Solution or Oral Powder in Children:

- Mix the solution or powder with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.
- Before administering RTV, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a **nonallergic** child peanut butter **or hazelnut chocolate spread** to coat the mouth.<sup>1</sup>
- After administration, give foods with strong tastes (e.g., maple syrup, cheese).
- Check a child's food allergy history before making these recommendations.
- Counsel caregivers or patients that the bad taste will not be completely masked.

#### Metabolism/Elimination

- Cytochrome P450 (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein.

#### Ritonavir Dosing in Patients with Hepatic Impairment:

- RTV is primarily metabolized by the liver.
- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- There are no data on RTV dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering RTV to patients with moderate-to-severe hepatic impairment.

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

- *Metabolism:* Ritonavir (RTV) is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P450 (CYP) 3A. Also, RTV is a CYP2D6 inhibitor and a CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer. RTV inhibits the intestinal transporter P-glycoprotein. There is potential for multiple drug interactions with RTV.
- Before RTV is administered, a patient's medication profile should be carefully reviewed for potential interactions with RTV and overlapping toxicities with other drugs.
- RTV and cobicistat **are not interchangeable**. The potential drug interactions for these drugs are different.<sup>2</sup>

- Avoid concomitant use of **corticosteroids, including** intranasal or inhaled fluticasone. Reduced elimination of steroids can increase steroid effects, leading to adrenal insufficiency.<sup>3,4</sup> Use caution when prescribing RTV with other inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking RTV requires an inhaled or intranasal corticosteroid.<sup>5,6</sup> Iatrogenic Cushing's syndrome and suppression of the hypothalamic-pituitary axis secondary to the drug interaction between RTV and local injection of triamcinolone has occurred.<sup>7,8</sup> 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.<sup>9</sup>

### Resistance

Resistance to RTV is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

### Pediatric Use

#### Approval

RTV has been approved by the Food and Drug Administration for use in the pediatric population.

#### Effectiveness in Practice

Use of RTV as the sole protease inhibitor (PI) in ARV therapy in children **is not recommended**. In both children and adults, RTV is recommended as a PK enhancer for use with other PIs. RTV is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PI.

#### Dosing

Pediatric dosing regimens, including boosted darunavir, atazanavir, and the coformulation lopinavir/ritonavir (LPV/r), are available. For more information about individual PIs, see other sections of the [Drug Appendix](#).

#### Toxicity

Full-dose RTV has been shown to prolong the PR interval in a study of healthy adults who were given RTV 400 mg twice daily.<sup>9</sup> Potentially life-threatening arrhythmias have been reported in premature infants who were treated with LPV/r; the use of LPV/r is generally not recommended before a gestational age of 42 weeks (see the [Lopinavir/Ritonavir](#) section).<sup>10,11</sup> Coadministration of RTV with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution, because it is unknown how coadministering any of these drugs with RTV will affect the PR interval. In addition, RTV should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as patients who have underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

## References

1. Morris JB, Tisi DA, Tan DCT, Worthington JH. Development and palatability assessment of norvir(R) (ritonavir) 100 mg powder for pediatric population. *Int J Mol Sci*. 2019;20(7). Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30959935>.

2. Marzolini C, Gibbons S, Khoo S, Back D. Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. *J Antimicrob Chemother.* 2016;71(7):1755-1758. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26945713>.
3. Bernecker C, West TB, Mansmann G, Scherbaum WA, Willenberg HS. Hypercortisolism caused by ritonavir associated inhibition of CYP 3A4 under inhalative glucocorticoid therapy. 2 case reports and a review of the literature. *Exp Clin Endocrinol Diabetes.* 2012;120(3):125-127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22328106>.
4. Peyro-Saint-Paul L, Besnier P, Demessine L, et al. Cushing's syndrome due to interaction between ritonavir or cobicistat and corticosteroids: a case-control study in the French Pharmacovigilance Database. *J Antimicrob Chemother.* 2019;74(11):3291-3294. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31369085>.
5. Boyd SD, Hadigan C, McManus M, et al. Influence of low-dose ritonavir with and without darunavir on the pharmacokinetics and pharmacodynamics of inhaled beclomethasone. *J Acquir Immune Defic Syndr.* 2013;63(3):355-361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23535292>.
6. Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV Med.* 2013;14(9):519-529. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23590676>.
7. Dubrocq G, Estrada A, Kelly S, Rakhmanina N. Acute development of Cushing syndrome in an HIV-infected child on atazanavir/ritonavir based antiretroviral therapy. *Endocrinol Diabetes Metab Case Rep.* 2017;2017. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29118985>.
8. Noe S, Jaeger H, Heldwein S. Adrenal insufficiency due to ritonavir-triamcinolone drug-drug interaction without preceding Cushing's syndrome. *Int J STD AIDS.* 2018;29(11):1136-1139. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29749880>.
9. Changes to Norvir labeling. *AIDS Patient Care STDS.* 2008;22(10):834-835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18924248>.
10. Lopriore E, Rozendaal L, Gelinck LB, Bokenkamp R, Boelen CC, Walther FJ. Twins with cardiomyopathy and complete heart block born to an HIV-infected mother treated with HAART. *AIDS.* 2007;21(18):2564-2565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18025905>.
11. McArthur MA, Kalu SU, Foulks AR, Aly AM, Jain SK, Patel JA. Twin preterm neonates with cardiac toxicity related to lopinavir/ritonavir therapy. *Pediatr Infect Dis J.* 2009;28(12):1127-1129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19820426>.

## 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 <sup>a</sup>	DOR	EFV	RPV	BIC <sup>a</sup>	DTG	EVG <sup>a</sup>	ATV	DRV	LPV <sup>b</sup>	COBI	RTV
<b>NRTI</b>																	
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												
<b>NRTI/NNRTI</b>																	
Atripla				X	X			X									
Complera				X	X				X								
Delstrigo		X			X		X										
Odefsey				X		X			X								
Symfi or Symfi Lo		X			X				X								
<b>NRTI/INSTI</b>																	
Biktarvy				X		X				X							
<b>Dovato</b>		<b>X</b>									<b>X</b>						
Triumeq	X	X									X						
<b>NNRTI/INSTI</b>																	
Juluca									X		X						
<b>NRTI/INSTI/COBI</b>																	
Genvoya				X		X						X				X	
Stribild				X	X							X				X	
<b>NRTI/PI/COBI</b>																	
Symtuza				X		X								X		X	
<b>PI/COBI</b>																	
Evotaz													X			X	
Prezcobix														X		X	
<b>PI/RTV</b>																	
Kaletra															X		X

## Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets

<sup>a</sup> 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.

<sup>b</sup> LPV is only available in FDC 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** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 1 of 4)

This table may include recently approved FDC tablets that have not yet been added to the individual drug sections in [Appendix A: Pediatric Antiretroviral Drug Information](#).

**General Considerations When Using FDC Tablets:**

- For children weighing  $\geq 25$  kg, the Panel recommends using one of the following single-tablet, once-daily regimens: Triumeq (ABC/DTG/3TC), Genvoya (EVG/c/FTC/TAF), or Biktarvy (BIC/FTC/TAF).
- ABC and TAF are favored over ZDV because of the 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 SMRs of 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 alternative to twice-daily ZDV plus 3TC or 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 over RPV.
- BIC and DTG, the second-generation INSTIs, have a higher barrier to resistance than the first-generation INSTIs EVG and RAL.
- For images of most of the FDC tablets listed in this table, see the Antiretroviral Medications section of the [National HIV Curriculum](#). In addition, a [resource from the United Kingdom](#) illustrates the relative sizes of FDC tablets and individual ARV drugs (see the [ARV Chart](#)). Although most of the drugs listed in that chart are the same as those in the United States, a few of the brand names are not the same as those listed in Appendix A, Table 2.
- FDC tablets and individual ARV drugs can also be looked up by drug name (brand name and generic) at [DailyMed](#); size is listed under the Ingredients and Appearance section.

**INSTI FDC Dosing for Children and Adolescents**

*Elvitegravir:*

- Genvoya (EVG/c/FTC/TAF) is approved by the FDA for children and adolescents weighing  $\geq 25$  kg.

*Dolutegravir:*

- The Panel recommends DTG 50 mg for children and adolescents weighing  $\geq 20$  kg (see the [Dolutegravir](#) section). The FDA-approved dose is DTG 35 mg for patients weighing  $\geq 30$  kg to 40 kg, and DTG 50 mg for patients weighing  $\geq 40$  kg.
- For children weighing  $\geq 25$  kg, DTG 50 mg can be given as Triumeq (ABC/DTG/3TC) in one large pill or as Descovy (FTC/TAF) plus DTG, which requires two small pills.
- **Exposure to DTG around the time of conception has been associated with a small, but significant, increase in the risk of infant NTDs.** Additional information and specific recommendations about the initiation and use of DTG in adolescents and women of childbearing potential and in those who are pregnant or who are trying to conceive are available in the Adult and Adolescent Antiretroviral Guidelines (see [Table 6b](#) and [Adolescents](#)

**Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 2 of 4)

and Young Adults with HIV) and in the Perinatal Guidelines (see [Teratogenicity](#), [Recommendations for Use of Antiretroviral Drugs During Pregnancy](#), and [Appendix D: Dolutegravir Counseling Guide for Health Care Providers](#)).

**Bictegravir:**

- Biktarvy (BIC/FTC/TAF) is now approved by the FDA for use in children and adolescents weighing  $\geq 25$  kg.

FDC by Class Brand name and generic <sup>a</sup> products, when available	FDC Components	Minimum Body Weight (kg) or Age <sup>b</sup>	Pill Size (mm x mm) or Largest Dimension (mm)	Food Requirements
<b>NRTI</b>				
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	<b>With an INSTI or NNRTI:</b> • 25 kg  <b>With a Boosted PI:</b> • 35 kg	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 (FDA) 30 kg (Panel) <sup>c</sup>	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
<b>NRTI/NNRTI</b>				
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 $\geq 12$ 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 $\geq 12$ years	15	Take with a meal

**Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents** (Last updated April 14, 2020; last reviewed April 14, 2020) (page 3 of 4)

<b>FDC by Class</b> Brand name and generic <sup>a</sup> products, when available	<b>FDC Components</b>	<b>Minimum Body Weight (kg) or Age<sup>b</sup></b>	<b>Pill Size (mm x mm) or Largest Dimension (mm)</b>	<b>Food Requirements</b>
<b>NRTI/NNRTI, continued</b>				
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 <sup>d</sup>	21	Take on an empty stomach
<b>NRTI/INSTI</b>				
Biktarvy	BIC 50 mg/FTC 200 mg/TAF 25 mg	25 kg	15 x 8	Take with or without food
Dovato	DTG 50 mg/3TC 300 mg	Adults <sup>e</sup>	19	Take with or without food
Triumeq	ABC 600 mg/DTG 50 mg/3TC 300 mg	40 kg (FDA) 25 kg (Panel) <sup>f</sup>	22 x 11	Take with or without food
<b>NNRTI/INSTI</b>				
Juluca	DTG 50 mg/RPV 25 mg	Adults	14	Take with a meal
<b>NRTI/INSTI/COBI</b>				
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 and ≥12 years <sup>g</sup>	20	Take with food
<b>NRTI/PI/COBI</b>				
Symtuza	DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg	40 kg	22	Take with food
<b>PI/COBI</b>				
Evotaz	ATV 300 mg/COBI 150 mg	35 kg	19	Take with food
Prezcobix	DRV 800 mg/COBI 150 mg	40 kg	23	Take with food
<b>PI/RTV</b>				
Kaletra	<b>LPV/r Oral Solution:</b> • LPV 80 mg/mL and RTV 20 mg/mL <b>Tablets:</b> • LPV 200 mg/RTV 50 mg • LPV 100 mg/RTV 25 mg	<b>Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days:</b> • No minimum weight	19	Take with or without food

<sup>a</sup> 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](https://www.dailymed.nlm.nih.gov/dailymed/).

<sup>b</sup> Minimum body weight and age are those recommended by the FDA, unless otherwise noted.

<sup>c</sup> Based on the current FDA-approved minimum body weights for the component drugs of Trizivir, the Panel suggests that Trizivir be used at a minimum body weight of ≥30 kg, although it is approved by the FDA for use in children and adolescents weighing ≥40 kg. However, the Panel **does not recommend** using regimens that only contain NRTIs, or using three-NRTI regimens, in children.

<sup>d</sup> Due to PK concerns, the Panel recommends caution when using Symfi Lo in children and adolescents who have SMRs of 1–3 and weigh ≥40 kg (see the [Efavirenz](#) section).

**Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents (Last updated April 14, 2020; last reviewed April 14, 2020)** (page 4 of 4)

<sup>e</sup> The Panel does not currently recommend using Dovato as a 2 drug complete regimen in adolescents and children. This FDC tablet could be used as part of a three-drug regimen in children who meet the minimum body weight requirements for each component drug.

<sup>f</sup> The Panel recommends using DTG 50 mg for children and adolescents weighing  $\geq 20$  kg based on available data. However, the doses of ABC and 3TC in Triumeq are too high for children weighing  $< 25$  kg (see the [Dolutegravir](#) section).

<sup>g</sup> Although Stribild is approved by the FDA for use in children and adolescents weighing  $\geq 35$  kg and aged  $\geq 12$  years, the Panel **does not recommend** using it in children or adolescents who have SMRs of 1–3.

**Key:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; LPV/r = lopinavir/ritonavir; N/A = information not available; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; the Panel = Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; 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<sup>2</sup> 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<sup>2</sup> body surface area every 12 hours

#### Pediatric Dose of Oral Solution (Age >8 Months):

- 120 mg/m<sup>2</sup> body surface area every 12 hours
- Dose range: 90–150 mg/m<sup>2</sup> body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naïve children ages 3 years to 21 years, 240 mg/m<sup>2</sup> 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.<sup>1</sup>
- *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.<sup>2</sup> 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

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availability of safer agents.

## **Dosing**

### *Standard Dose in Children Aged >8 Months*

The standard dose of didanosine oral solution in children aged >8 months is 120 mg/m<sup>2</sup> of body surface area twice daily.<sup>3,4</sup> Doses higher than 180 mg/m<sup>2</sup> of body surface area twice daily are associated with increased toxicity.<sup>5</sup>

### *Special Considerations for Children Aged 2 Weeks to <8 Months*

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m<sup>2</sup> of body surface area per dose twice daily. However, because pharmacokinetic (PK) differences in younger infants (aged 2 weeks–3 months) compared with older children raise concerns for increased toxicity in this younger age group, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends a dose of 50 mg/m<sup>2</sup> of body surface area twice daily for infants aged 2 weeks to 3 months, with an increase to 100 mg/m<sup>2</sup> of body surface area per dose twice daily at 3 months, and finally increasing to 120 mg/m<sup>2</sup> of body surface area per dose twice daily at age 8 months (as discussed above).

### *Frequency of Administration (Once Daily or Twice Daily)*

In those aged >3 years, a once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing of 240 mg/m<sup>2</sup> of body surface area.<sup>6</sup>

### *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.<sup>7</sup> 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.<sup>8,9</sup> 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.<sup>10</sup>

## **References**

1. Scherpbier HJ, Terpstra V, Pajkrt D, et al. Noncirrhotic portal hypertension in perinatally HIV-infected adolescents treated with didanosine-containing antiretroviral regimens in childhood. *Pediatr Infect Dis J*. 2016. Available at <http://www.ncbi.nlm.nih.gov/pubmed/27167116>.
2. Hleyhel M, Goujon S, Delteil C, et al. Risk of cancer in children exposed to didanosine *in utero*. *AIDS*. 2016;30(8):1245-1256. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26854809>.
3. Fletcher CV, Brundage RC, Rimmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother*. 2000;44(4):1029-1034. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10722507>.
4. Nacro B, Zoure E, Hien H, et al. Pharmacology and immuno-virologic efficacy of once-a-day HAART in African HIV-infected children: ANRS 12103 phase II trial. *Bull World Health Organ*. 2011;89(6):451-458. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21673861>.
5. Butler KM, Husson RN, Balis FM, et al. Dideoxyinosine in children with symptomatic human immunodeficiency virus infection. *N Engl J Med*. 1991;324(3):137-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1670591>.
6. King JR, Nachman S, Yogev R, et al. Single-dose pharmacokinetics of enteric-coated didanosine in HIV-infected children. *Antivir Ther*. 2002;7(4):267-270. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12553481>.

7. Stevens RC, Rodman JH, Yong FH, Carey V, Knupp CA, Frenkel LM. Effect of food and pharmacokinetic variability on didanosine systemic exposure in HIV-infected children. Pediatric AIDS Clinical Trials Group Protocol 144 Study Team. *AIDS Res Hum Retroviruses*. 2000;16(5):415-421. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10772527>.
8. Sanchez-Conde M, Palacios R, Sanz J, et al. Efficacy and safety of a once daily regimen with efavirenz, lamivudine, and didanosine, with and without food, as initial therapy for HIV Infection: the ELADI study. *AIDS Res Hum Retroviruses*. 2007;23(10):1237-1241. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17961110>.
9. Hernandez-Novoa B, Antela A, Gutierrez C, et al. Effect of food on the antiviral activity of didanosine enteric-coated capsules: a pilot comparative study. *HIV Med*. 2008;9(4):187-191. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18298579>.
10. Scherpbier HJ, Bekker V, Pajkrt D, Jurriaans S, Lange JM, Kuijpers TW. Once-daily highly active antiretroviral therapy for HIV-infected children: safety and efficacy of an efavirenz-containing regimen. *Pediatrics*. 2007;119(3):e705-715. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17308244>.

## 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).<sup>1</sup> 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).<sup>2</sup>

### **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<sup>3</sup> 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<sup>2</sup> 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).<sup>4</sup> 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<sup>2</sup> of body surface area dose independent of age group, body weight, body surface area, and sexual maturation.<sup>5</sup> 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<sup>2</sup> 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<sub>log</sub> 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<sub>log</sub> decrease in HIV RNA) at Week 96. Most children had local injection site reactions.<sup>6</sup> 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<sub>10</sub> copies/mL (n = 32) and increase in CD4 cell count was 106 cells/mm<sup>3</sup> (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<sup>3</sup> in children and 84 cells/mm<sup>3</sup> 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.<sup>2</sup>

## References

1. Kousignian I, Launay O, Mayaud C, et al. Does enfuvirtide increase the risk of bacterial pneumonia in patients receiving combination antiretroviral therapy? *J Antimicrob Chemother.* 2010;65(1):138-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19903719>.
2. Wiznia A, Church J, Emmanuel P, et al. Safety and efficacy of enfuvirtide for 48 weeks as part of an optimized antiretroviral regimen in pediatric human immunodeficiency virus 1-infected patients. *Pediatr Infect Dis J.* 2007;26(9):799-805. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17721374>.
3. Feiterna-Sperling C, Walter H, Wahn V, Kleinkauf N. A 12-year-old boy with multidrug-resistant human immunodeficiency virus type 1 successfully treated with HAART including ritonavir-boosted tipranavir oral solution and enfuvirtide. *Eur J Med Res.* 2009;14(1):44-46. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19258211>.
4. Church JA, Cunningham C, Hughes M, et al. Safety and antiretroviral activity of chronic subcutaneous administration of T-20 in human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2002;21(7):653-659. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12237598>.
5. Bellibas SE, Siddique Z, Dorr A, et al. Pharmacokinetics of enfuvirtide in pediatric human immunodeficiency virus 1-infected patients receiving combination therapy. *Pediatr Infect Dis J.* 2004;23(12):1137-1141. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15626952>.
6. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J.* 2004;23(8):713-718. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15295220>.

# 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  $\geq 4$  weeks and for treatment-experienced infants  $\geq 6$  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 $\geq 6$ Months to 18 Years):

#### Twice-Daily Dose Regimens by Weight for Pediatric Patients $\geq 6$ Months Using Fosamprenavir Oral Suspension with Ritonavir

Weight	Dose (Both Drugs Twice Daily <sup>a</sup> 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
$\geq 20$ kg	Fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose

<sup>a</sup> 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  $\geq 39$  kg. Ritonavir tablets can be used in patients weighing  $\geq 33$  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).<sup>1</sup>

### 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

*Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*

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Panel) recommends use only in children aged  $\geq 6$  months. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naïve 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.<sup>2</sup>

### *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-naïve children aged 2 to 18 years,<sup>3,4</sup> 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-naïve infants as young as age 4 weeks and in treatment-experienced infants as young as age 6 months.<sup>1,5</sup> 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 <sub>0-24h</sub> (mcg*hr/mL) Except Where Noted	C <sub>min</sub> (mcg/mL)
Infants Aged $< 6$ Months	FPV 45 mg/kg plus RTV 10 mg/kg twice daily	26.6 <sup>a</sup>	0.86
Children Aged 2 Years to $< 6$ Years	FPV 30 mg/kg twice daily (no RTV)	22.3 <sup>a</sup>	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 $\geq 20$ 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

<sup>a</sup> AUC<sub>0-12</sub> (mcg\*hr/mL)

**Key to Acronyms:** AUC<sub>0-24h</sub> = area under the curve for 24 hours post-dose; C<sub>min</sub> = 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<sub>min</sub> are not available.

## References

1. Fosamprenavir [package insert]. Food and Drug Administration. 2016. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/022116s023\\_21548-s391bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022116s023_21548-s391bl.pdf).
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2016. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>.
3. Chadwick E, Borkowsky W, Fortuny C, et al. Safety and antiviral activity of fosamprenavir/ritonavir once daily regimens in HIV-infected pediatric subjects ages 2 to 18 years (48-week interim data, study apv20003). Presented at:

14th Conference on Retroviruses and Opportunistic Infections. 2007. Los Angeles, CA.

4. Fortuny C, Duiculescu D, Cheng K, et al. Pharmacokinetics and 48-week safety and antiviral activity of fosamprenavir-containing regimens in HIV-infected 2- to 18-year-old children. *Pediatr Infect Dis J*. 2014;33(1):50-56. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23811744>.
5. Cotton M, Cassim H, Pavia-Ruz N, et al. Pharmacokinetics, safety and antiviral activity of fosamprenavir/ritonavir-containing regimens in HIV-infected children aged 4 weeks to 2 years-48-week study data. *Pediatr Infect Dis J*. 2014;33(1):57-62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23811743>.

## 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<sup>2</sup> 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 ( $\geq 48$  oz of fluid daily in adult patients).
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86°F) in original container with desiccant.

#### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate

#### Indinavir Dosing in Patients with Hepatic Impairment:

- Dose should be decreased in patients with mild-to-moderate hepatic impairment (recommended dose for adults is 600 mg indinavir every 8 hours). No dosing information is available for children with any degree of hepatic impairment or for adults with severe hepatic impairment.

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

- **Metabolism:** Cytochrome P450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions with indinavir.
- Avoid other drugs that cause hyperbilirubinemia, such as atazanavir.
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with indinavir.

### **Major Toxicities**

- **More common:** Nephrolithiasis/urolithiasis with indinavir crystal deposit is reported more frequently in children (29%) than in adults (12.4%).<sup>1</sup> Interstitial nephritis and urothelial inflammation has been commonly reported in adults.<sup>2</sup> 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.<sup>3</sup> 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<sup>2</sup> 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.<sup>4-7</sup> Studies that investigated a range of indinavir/ritonavir doses in small groups of children have shown that indinavir 500 mg/m<sup>2</sup> body surface area plus ritonavir 100 mg/m<sup>2</sup> body surface area twice daily is probably too high,<sup>8</sup> that indinavir 234 to 250 mg/m<sup>2</sup> body surface area plus low-dose ritonavir twice daily is too low,<sup>9,10</sup> and that indinavir 400 mg/m<sup>2</sup> body surface area plus ritonavir 100 to 125 mg/m<sup>2</sup> 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.<sup>10-12</sup>

## **References**

1. Indinavir [package insert]. Food and Drug Administration. 2015. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/020685s077lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020685s077lbl.pdf).
2. Kopp JB, Falloon J, Filie A, et al. Indinavir-associated interstitial nephritis and urothelial inflammation: clinical

and cytologic findings. *Clin Infect Dis*. 2002;34(8):1122-1128. Available at <https://www.ncbi.nlm.nih.gov/pubmed/11915002>.

3. Van Dyke RB, Patel K, Siberry GK, et al. Antiretroviral treatment of US children with perinatally acquired HIV infection: temporal changes in therapy between 1991 and 2009 and predictors of immunologic and virologic outcomes. *J Acquir Immune Defic Syndr*. 2011;57(2):165-173. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21407086>.
4. Burger DM, van Rossum AM, Hugen PW, et al. Pharmacokinetics of the protease inhibitor indinavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother*. 2001;45(3):701-705. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11181346>.
5. Fletcher CV, Brundage RC, Rimmel RP, et al. Pharmacologic characteristics of indinavir, didanosine, and stavudine in human immunodeficiency virus-infected children receiving combination therapy. *Antimicrob Agents Chemother*. 2000;44(4):1029-1034. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10722507>.
6. Gatti G, Vigano A, Sala N, et al. Indinavir pharmacokinetics and pharmacodynamics in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2000;44(3):752-755. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10681350>.
7. Mueller BU, Sleasman J, Nelson RP, Jr., et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics*. 1998;102(1 Pt 1):101-109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9651421>.
8. van Rossum AM, Dieleman JP, Fraaij PL, et al. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. *Pediatrics*. 2002;110(2 Pt 1):e19. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12165618>.
9. Plipat N, Cressey TR, Vanprapar N, Chokephaibulkit K. Efficacy and plasma concentrations of indinavir when boosted with ritonavir in human immunodeficiency virus-infected Thai children. *Pediatr Infect Dis J*. 2007;26(1):86-88. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17195716>.
10. Curras V, Hocht C, Mangano A, et al. Pharmacokinetic study of the variability of indinavir drug levels when boosted with ritonavir in HIV-infected children. *Pharmacology*. 2009;83(1):59-66. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19052483>.
11. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother*. 2004;48(5):1904-1907. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15105157>.
12. Fraaij PL, Bergshoeff AS, van Rossum AM, Hartwig NG, Burger DM, de Groot R. Changes in indinavir exposure over time: a case study in six HIV-1-infected children. *J Antimicrob Chemother*. 2003;52(4):727-730. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12917234>.

## 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 $\geq 2$ 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  $\geq 2$  years. Given the higher variability of nelfinavir plasma concentrations in infants and younger children,<sup>1,2</sup> 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.<sup>3-10</sup> 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.<sup>8,10,11</sup> 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.<sup>12-14</sup> The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.<sup>3,15</sup>

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,<sup>16</sup> 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.<sup>17,18</sup> Furthermore, CYP2C19 genotype has been shown to affect nelfinavir PK and the virologic responses in children with HIV.<sup>12</sup>

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.<sup>19-21</sup>

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.<sup>22</sup> Children in the group with  $C_{\text{trough}} < 0.8$  mcg/mL were younger than the children in the group with  $C_{\text{trough}} > 0.8$  mcg/mL (median ages in these groups were 3.8 years and 8.3 years, respectively).<sup>22</sup> 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.<sup>18,19,23,24</sup> Pediatric and

adolescent patients may require doses higher than those recommended in adults to achieve higher plasma nelfinavir exposure.

## References

1. Capparelli EV, Sullivan JL, Mofenson L, et al. Pharmacokinetics of nelfinavir in human immunodeficiency virus-infected infants. *Pediatr Infect Dis J*. 2001;20(8):746-751. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11734735>.
2. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr*. 2005;39(2):189-194. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15905735>.
3. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. 2004;18(2):237-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15075541>.
4. King JR, Nachman S, Yogev R, et al. Efficacy, tolerability and pharmacokinetics of two nelfinavir-based regimens in human immunodeficiency virus-infected children and adolescents: pediatric AIDS clinical trials group protocol 403. *Pediatr Infect Dis J*. 2005;24(10):880-885. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16220085>.
5. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
6. Krogstad P, Wiznia A, Luzuriaga K, et al. Treatment of human immunodeficiency virus 1-infected infants and children with the protease inhibitor nelfinavir mesylate. *Clin Infect Dis*. 1999;28(5):1109-1118. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10452644>.
7. Luzuriaga K, McManus M, Mofenson L, et al. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med*. 2004;350(24):2471-2480. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15190139>.
8. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002;359(9308):733-740. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=11888583&query\\_hl=42](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11888583&query_hl=42).
9. Resino S, Larru B, Maria Bellon J, et al. Effects of highly active antiretroviral therapy with nelfinavir in vertically HIV-1 infected children: 3 years of follow-up. Long-term response to nelfinavir in children. *BMC Infect Dis*. 2006;6:107. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16834769>.
10. Scherpbier HJ, Bekker V, van Leth F, Jurriaans S, Lange JM, Kuijpers TW. Long-term experience with combination antiretroviral therapy that contains nelfinavir for up to 7 years in a pediatric cohort. *Pediatrics*. 2006;117(3):e528-536. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16481448>.
11. Nelfinavir [package insert]. Food and Drug Administration. 2011. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/020778s035,020779s056,021503s017lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020778s035,020779s056,021503s017lbl.pdf).
12. Saitoh A, Capparelli E, Aweeka F, et al. CYP2C19 genetic variants affect nelfinavir pharmacokinetics and virologic response in HIV-1-infected children receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2010;54(3):285-289. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19890215>.
13. Wu H, Lathey J, Ruan P, et al. Relationship of plasma HIV-1 RNA dynamics to baseline factors and virological responses to highly active antiretroviral therapy in adolescents (aged 12–22 years) infected through high-risk behavior. *J Infect Dis*. 2004;189(4):593-601. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=14767811&query\\_hl=31](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14767811&query_hl=31).
14. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002;346(26):2039-2046. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12087139>.
15. Regazzi MB, Seminari E, Villani P, et al. Nelfinavir suspension obtained from nelfinavir tablets has equivalent

pharmacokinetic profile. *J Chemother.* 2001;13(5):569-574. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11760223>.

16. Gatti G, Castelli-Gattinara G, Cruciani M, et al. Pharmacokinetics and pharmacodynamics of nelfinavir administered twice or thrice daily to human immunodeficiency virus type 1-infected children. *Clin Infect Dis.* 2003;36(11):1476-1482. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12766843>.
17. Hirt D, Urien S, Jullien V, et al. Age-related effects on nelfinavir and M8 pharmacokinetics: a population study with 182 children. *Antimicrob Agents Chemother.* 2006;50(3):910-916. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16495250>.
18. Crommentuyn KM, Scherpbier HJ, Kuijpers TW, Mathot RA, Huitema AD, Beijnen JH. Population pharmacokinetics and pharmacodynamics of nelfinavir and its active metabolite M8 in HIV-1-infected children. *Pediatr Infect Dis J.* 2006;25(6):538-543. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16732153>.
19. Burger DM, Hugen PW, Aarnoutse RE, et al. Treatment failure of nelfinavir-containing triple therapy can largely be explained by low nelfinavir plasma concentrations. *Ther Drug Monit.* 2003;25(1):73-80. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=12548148&query\\_hl=15](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12548148&query_hl=15).
20. Gonzalez de Requena D, Nunez M, de Mendoza C, Jimenez-Nacher I, Soriano V. Nelfinavir plasma concentrations in patients experiencing early failure with nelfinavir-containing triple combinations. *AIDS.* 2003;17(3):442-444. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12556700>.
21. Pellegrin I, Breilh D, Montestruc F, et al. Virologic response to nelfinavir-based regimens: pharmacokinetics and drug resistance mutations (VIRAPHAR study). *AIDS.* 2002;16(10):1331-1340. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12131209>.
22. Burger DM, Bergshoeff AS, De Groot R, et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L improves virologic response in HIV-1-infected children. *J Pediatr.* 2004;145(3):403-405. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15343199>.
23. Burger D, Hugen P, Reiss P, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS.* 2003;17(8):1157-1165. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12819517>.
24. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther.* 2008;83(2):300-306. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17609682>.

## 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

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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.<sup>1</sup>

#### *Efficacy*

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors and other protease inhibitors in children with HIV.<sup>2-9</sup> 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.<sup>10</sup> In children aged  $\geq 2$  years, a dose of saquinavir 50 mg/kg twice daily in combination with ritonavir and lopinavir/ritonavir resulted in steady-state plasma trough concentrations ( $C_{\text{trough}}$ ) similar to those seen adults.<sup>9,11</sup> 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.<sup>1,12</sup> 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.<sup>1,12</sup> 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.

## **References**

1. Saquinavir [package insert]. Food and Drug Administration. 2015. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/020628s43-021785s19lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020628s43-021785s19lbl.pdf).
2. Ananworanich J, Kosalaraksa P, Hill A, et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/

- lopinavir/ritonavir in nucleoside-pretreated children. *Pediatr Infect Dis J*. 2005;24(10):874-879. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16220084>.
3. De Luca M, Miccinesi G, Chiappini E, Zappa M, Galli L, De Martino M. Different kinetics of immunologic recovery using nelfinavir or lopinavir/ritonavir-based regimens in children with perinatal HIV-1 infection. *Int J Immunopathol Pharmacol*. 2005;18(4):729-735. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16388722>.
  4. Grub S, Delora P, Ludin E, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther*. 2002;71(3):122-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11907486>.
  5. Hoffmann F, Notheis G, Wintergerst U, Eberle J, Gurtler L, Belohradsky BH. Comparison of ritonavir plus saquinavir and nelfinavir plus saquinavir-containing regimens as salvage therapy in children with human immunodeficiency type 1 infection. *Pediatr Infect Dis J*. 2000;19(1):47-51. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10643850>.
  6. Kline MW, Brundage RC, Fletcher CV, et al. Combination therapy with saquinavir soft gelatin capsules in children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2001;20(7):666-671. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11465838>.
  7. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scandinavian journal of infectious diseases*. 2002;34(1):41-44. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11874163>.
  8. Robbins BL, Capparelli EV, Chadwick EG, et al. Pharmacokinetics of high-dose lopinavir-ritonavir with and without saquinavir or nonnucleoside reverse transcriptase inhibitors in human immunodeficiency virus-infected pediatric and adolescent patients previously treated with protease inhibitors. *Antimicrob Agents Chemother*. 2008;52(9):3276-3283. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18625762>.
  9. Bunupuradah T, van der Lugt J, Kosalaraksa P, et al. Safety and efficacy of a double-boosted protease inhibitor combination, saquinavir and lopinavir/ritonavir, in pretreated children at 96 weeks. *Antivir Ther*. 2009;14(2):241-248. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19430099>.
  10. Haznedar J, Zhang A, Labriola-Tompkins E, et al. A pharmacokinetic study of ritonavir-boosted saquinavir in HIV-infected children 4 months to <6 years old. Presented at: 17th Conference on Retroviruses and Opportunistic Infections (CROI); February 16-19, 2010; San Francisco, CA.
  11. Kosalaraksa P, Bunupuradah T, Engchanil C, et al. Double boosted protease inhibitors, saquinavir, and lopinavir/ritonavir, in nucleoside pretreated children at 48 weeks. *Pediatr Infect Dis J*. 2008;27(7):623-628. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18520443>.
  12. Zhang X, Jordan P, Cristea L, et al. Thorough QT/QTc study of ritonavir-boosted saquinavir following multiple-dose administration of therapeutic and supratherapeutic doses in healthy participants. *J Clin Pharmacol*. 2012;52(4):520-529. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21558456>.

## 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 $\geq 14$ Days and Weighing $< 30$ kg)

##### Dose:

- 1 mg/kg per dose twice daily

#### Adolescent (Weighing $\geq 30$ 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.<sup>1-3</sup> 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.<sup>4</sup>
- *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  $\geq 14$  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.<sup>5-11</sup> 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-naïve children.<sup>12-15</sup> 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.<sup>16</sup> 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.<sup>17,18</sup>

### **Toxicity**

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.<sup>19,20</sup> 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.<sup>20</sup>

#### *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.<sup>21-24</sup> 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.<sup>25-33</sup> Improvements in (or resolution of) lipodystrophy were reported in 22.9% to 73% of cases after discontinuation of stavudine in two separate studies.<sup>30,34</sup>

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine.<sup>1-3</sup>

#### *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.<sup>1,35-37</sup> 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.<sup>38</sup>

#### *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.<sup>39,40</sup> 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.<sup>41-45</sup> 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.<sup>46</sup> 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.<sup>47,48</sup> 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.<sup>49</sup>

## References

1. Haugaard SB, Andersen O, Pedersen SB, et al. Depleted skeletal muscle mitochondrial DNA, hyperlactatemia, and decreased oxidative capacity in HIV-infected patients on highly active antiretroviral therapy. *J Med Virol*. 2005;77(1):29-38. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16032748>.
2. Koh MT. Unrecognized near-fatal hyperlactatemia in an HIV-infected infant exposed to nucleoside reverse transcriptase inhibitors. *Int J Infect Dis*. 2007;11(1):85-86. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16581278>.
3. Hernandez Perez E, Dawood H. Stavudine-induced hyperlactatemia/lactic acidosis at a tertiary communicable diseases clinic in South Africa. *J Int Assoc Physicians AIDS Care (Chic)*. 2010;9(2):109-112. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20484736>.
4. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS One*. 2011;6(4):e18736. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21494566>.
5. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS*. 2004;18(2):237-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15075541>.
6. Kline MW, Dunkle LM, Church JA, et al. A phase I/II evaluation of stavudine (d4T) in children with human immunodeficiency virus infection. *Pediatrics*. 1995;96(2 Pt 1):247-252. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7630678>.
7. Kline MW, Fletcher CV, Federici ME, et al. Combination therapy with stavudine and didanosine in children with advanced human immunodeficiency virus infection: pharmacokinetic properties, safety, and immunologic and virologic effects. *Pediatrics*. 1996;97(6 Pt 1):886-890. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8657531>.
8. Kline MW, Van Dyke RB, Lindsey JC, et al. Combination therapy with stavudine (d4T) plus didanosine (ddI) in children with human immunodeficiency virus infection. The Pediatric AIDS Clinical Trials Group 327 Team. *Pediatrics*. 1999;103(5):e62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10224206>.
9. Krogstad P, Lee S, Johnson G, et al. Nucleoside-analogue reverse-transcriptase inhibitors plus nevirapine, nelfinavir, or ritonavir for pretreated children infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2002;34(7):991-1001. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11880966>.
10. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. 2000;283(4):492-498. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10659875>.
11. Yogev R, Lee S, Wiznia A, et al. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2002;21(2):119-125. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11840078>.
12. Bolton-Moore C, Mubiana-Mbewe M, Cantrell RA, et al. Clinical outcomes and CD4 cell response in children receiving antiretroviral therapy at primary health care facilities in Zambia. *JAMA*. 2007;298(16):1888-1899. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17954540>.
13. Janssens B, Raleigh B, Soeung S, et al. Effectiveness of highly active antiretroviral therapy in HIV-positive children: evaluation at 12 months in a routine program in Cambodia. *Pediatrics*. 2007;120(5):e1134-1140. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17954553>.
14. Kanya MR, Mayanja-Kizza H, Kambugu A, et al. Predictors of long-term viral failure among ugandan children and adults treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2007;46(2):187-193. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17693883>.
15. Zhang F, Haberer JE, Zhao Y, et al. Chinese pediatric highly active antiretroviral therapy observational cohort: a 1-year analysis of clinical, immunologic, and virologic outcomes. *J Acquir Immune Defic Syndr*. 2007;46(5):594-598. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18043313>.
16. Okechukwu AA, Gambo D, Okechukwu IO. Prevalence of anaemia in HIV-infected children at the University of Abuja Teaching Hospital, Gwagwalada. *Niger J Med*. 2010;19(1):50-57. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20232757>.

17. Kenny J, Musiime V, Judd A, Gibb D. Recent advances in pharmacovigilance of antiretroviral therapy in HIV-infected and exposed children. *Curr Opin HIV AIDS*. 2012;7(4):305-316. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22678488>.
18. Palmer M, Chersich M, Moultrie H, Kuhn L, Fairlie L, Meyers T. Frequency of stavudine substitution due to toxicity in children receiving antiretroviral treatment in sub-Saharan Africa. *AIDS*. 2013;27(5):781-785. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23169331>.
19. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med*. 2003;349(24):2293-2303. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14668455>.
20. Van Dyke RB, Wang L, Williams PL, Pediatric ACTGCT. Toxicities associated with dual nucleoside reverse-transcriptase inhibitor regimens in HIV-infected children. *J Infect Dis*. 2008;198(11):1599-1608. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19000014>.
21. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipodystrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. *AIDS*. 2002;16(18):2447-2454. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12461419>.
22. European Paediatric Lipodystrophy Group. Antiretroviral therapy, fat redistribution and hyperlipidaemia in HIV-infected children in Europe. *AIDS*. 2004;18(10):1443-1451. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=15199321&query\\_hl=60](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15199321&query_hl=60).
23. Ene L, Goetghebuer T, Hainaut M, Peltier A, Toppet V, Levy J. Prevalence of lipodystrophy in HIV-infected children: a cross-sectional study. *Eur J Pediatr*. 2007;166(1):13-21. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16896646>.
24. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. 2009;23(9):1109-1118. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19417580>.
25. Jacobson DL, Patel K, Siberry GK, et al. Body fat distribution in perinatally HIV-infected and HIV-exposed but uninfected children in the era of highly active antiretroviral therapy: outcomes from the Pediatric HIV/AIDS Cohort Study. *Am J Clin Nutr*. 2011;94(6):1485-1495. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22049166>.
26. Dapena M, Jimenez B, Noguera-Julian A, et al. Metabolic disorders in vertically HIV-infected children: future adults at risk for cardiovascular disease. *J Ped Endocrin Metab*. 2012;25(5-6):529-535. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22876550>.
27. Alam N, Cortina-Borja M, Goetghebuer T, et al. Body fat abnormality in HIV-infected children and adolescents living in Europe: prevalence and risk factors. *J Acquir Immune Defic Syndr*. 2012;59(3):314-324. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22205436>.
28. Kinabo GD, Sprengers M, Msuya LJ, et al. Prevalence of lipodystrophy in HIV-infected children in Tanzania on highly active antiretroviral therapy. *Pediatr Infect Dis J*. 2013;32(1):39-44. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23038217>.
29. Piloya T, Bakeera-Kitaka S, Kekitiinwa A, Kanya MR. Lipodystrophy among HIV-infected children and adolescents on highly active antiretroviral therapy in Uganda: a cross sectional study. *J Int AIDS Soc*. 2012;15(2):17427. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22814353>.
30. Aurpibul L, Puthanakit T, Taejaroenkul S, et al. Improvement of lipodystrophy in children after substitution of stavudine with zidovudine in NNRTI-based antiretroviral therapy, Abstract #CDB437. Presented at: 6th IAS Conference on HIV Pathogenesis Treatment and Prevention. 2011. Rome, Italy.
31. Innes SEV, van Niekerk M, Rabie H, et al. Prevalence and risk factors for lipodystrophy among pre-pubertal African children on HAART, Abstract #CDB430. Presented at: 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. 2011. Rome, Italy.
32. Cohen S, Innes S, Geelen SP, et al. Long-term changes of subcutaneous fat mass in HIV-infected children on antiretroviral therapy: a retrospective analysis of longitudinal data from two pediatric HIV-cohorts. *PLoS One*. 2015;10(7):e0120927. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26148119>.
33. Fortuin-de Smidt M, de Waal R, Cohen K, et al. First-line antiretroviral drug discontinuations in children. *PLoS One*. 2017;12(2):e0169762. Available at <https://www.ncbi.nlm.nih.gov/pubmed/28192529>.

34. Sawawiboon N, Wittawatmongkol O, Phongsamart W, Prasitsuebsai W, Lapphra K, Chokephaibulkit K. Lipodystrophy and reversal of facial lipoatrophy in perinatally HIV-infected children and adolescents after discontinuation of stavudine. *Int J STD AIDS*. 2012;23(7):497-501. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22844004>.
35. Blanco F, Garcia-Benayas T, Jose de la Cruz J, Gonzalez-Lahoz J, Soriano V. First-line therapy and mitochondrial damage: different nucleosides, different findings. *HIV Clin Trials*. 2003;4(1):11-19. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12577192>.
36. Cherry CL, Gahan ME, McArthur JC, et al. Exposure to dideoxynucleosides is reflected in lowered mitochondrial DNA in subcutaneous fat. *J Acquir Immune Defic Syndr*. 2002;30(3):271-277. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=12131563](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12131563).
37. Sanchez-Conde M, de Mendoza C, Jimenez-Nacher I, Barreiro P, Gonzalez-Lahoz J, Soriano V. Reductions in stavudine dose might ameliorate mitochondrial-associated complications without compromising antiviral activity. *HIV Clin Trials*. 2005;6(4):197-202. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16214736>.
38. Crain MJ, Chernoff MC, Oleske JM, et al. Possible mitochondrial dysfunction and its association with antiretroviral therapy use in children perinatally infected with HIV. *J Infect Dis*. 2010;202(2):291-301. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20533872>.
39. World Health Organization. Toxicity of reduced and standard doses of d4T. 2009. Available at [http://www.who.int/hiv/pub/arv/rapid\\_advice\\_art.pdf](http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf).
40. World Health Organization. Rapid advice. Antiretroviral therapy for HIV infection in adults and adolescents. 2009. Available at [http://www.who.int/hiv/pub/arv/rapid\\_advice\\_art.pdf](http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf).
41. Pahuja M, Glesby M, Grobler A, et al. Effects of a reduced dose of stavudine (d4T) on the incidence and severity of peripheral neuropathy in PLHIV in South Africa. Abstract #WEPE0149. Presented at: IAS-AIDS. 2010.
42. Hoffmann CJ, Charalambous S, Fielding KL, et al. HIV suppression with stavudine 30 mg versus 40 mg in adults over 60 kg on antiretroviral therapy in South Africa. *AIDS*. 2009;23(13):1784-1786. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19491652>.
43. Pujades-Rodriguez M, Dantony E, Pinoges L, et al. Toxicity associated with stavudine dose reduction from 40 to 30 mg in first-line antiretroviral therapy. *PLoS One*. 2011;6(11):e28112. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22132226>.
44. Brennan A, Maskew M, Sanne I, Fox M. The effect of 30 vs. 40 mg of stavudine vs. tenofovir on treatment outcomes amongst HIV+ patients: Johannesburg, South Africa. Abstract # 1098. Presented at: Conference on Retroviruses and Opportunistic Infections. 2013. Atlanta, GA.
45. Maskew M, Westreich D, Fox MP, Maotie T, Sanne IM. Effectiveness and safety of 30 mg versus 40 mg stavudine regimens: a cohort study among HIV-infected adults initiating HAART in South Africa. *J Int AIDS Soc*. 2012;15(1):13. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22410312>.
46. Kaul S, Kline MW, Church JA, Dunkle LM. Determination of dosing guidelines for stavudine (2',3'-didehydro-3'-deoxythymidine) in children with human immunodeficiency virus infection. *Antimicrob Agents Chemother*. 2001;45(3):758-763. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11181356>.
47. Sy SK, Innes S, Derendorf H, Cotton MF, Rosenkranz B. Estimation of intracellular concentration of stavudine triphosphate in HIV-infected children given a reduced dose of 0.5 milligrams per kilogram twice daily. *Antimicrob Agents Chemother*. 2014;58(2):1084-1091. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24295968>.
48. Sy SK, Malmberg R, Matsushima A, et al. Effect of reducing the paediatric stavudine dose by half: a physiologically-based pharmacokinetic model. *Int J Antimicrob Agents*. 2015;45(4):413-419. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25697412>.
49. Innes S, Norman J, Smith P, et al. Bioequivalence of dispersed stavudine: opened versus closed capsule dosing. *Antivir Ther*. 2011;16(7):1131-1134. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22024529>.

## 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-naïve patients

#### Body Surface Area Dosing:

- Tipranavir/ritonavir (TPV/r) 375 mg/m<sup>2</sup>/150 mg/m<sup>2</sup>, 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-naïve 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).<sup>1</sup> 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).<sup>2</sup> This study enrolled 110 treatment-experienced children (with the exception of three treatment-naïve 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<sup>2</sup> 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.<sup>3</sup> 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.<sup>3</sup>

#### **Pharmacokinetics**

PK evaluation of the liquid formulation at steady state in children was assessed.<sup>4</sup> In children aged 2 to <12 years, a dose of TPV/r 290 mg/115 mg/m<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> BSA twice daily is recommended.

#### **Toxicity**

AEs were similar between treatment groups in the multicenter, pediatric study.<sup>2</sup> 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.<sup>3</sup>

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%).<sup>2</sup> Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.<sup>5</sup>

## References

1. Courter JD, Teevan CJ, Li MH, Giroto JE, Salazar JC. Role of tipranavir in treatment of patients with multidrug-resistant HIV. *Ther Clin Risk Manag*. 2010;6:431-441. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20957134>.
2. Salazar JC, Cahn P, Yogeve R, et al. Efficacy, safety and tolerability of tipranavir coadministered with ritonavir in HIV-1-infected children and adolescents. *AIDS*. 2008;22(14):1789-1798. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18753862>.
3. Salazar JC, Cahn P, Della Negra M, et al. Efficacy and safety of tipranavir coadministered with ritonavir in HIV-1-infected children and adolescents: 5 years of experience. *Pediatr Infect Dis J*. 2014;33(4):396-400. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23995585>.
4. Sabo J, Cahn P, Della Negra M, et al. Population pharmacokinetic (PK) assessment of systemic steady-state tipranavir (TPV) concentrations for HIV+ pediatric patients administered tipranavir/ritonavir (TPV/r) 290/115 mg/m<sup>2</sup> and 375/150 mg/m<sup>2</sup> BID (BI 1192.14 and PACTG 1051 study team). Presented at: 13th Conference on Retroviruses and Opportunistic Infections (CROI). 2006. Denver, CO.
5. Tipranavir [package insert]. Food and Drug Administration. 2015. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2005/021814lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021814lbl.pdf).

## Appendix B: Acronyms (Last updated April 16, 2019; last reviewed April 16, 2019)

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Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
BIC	bictegravir
COBI or /c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
<b>DOR</b>	<b>doravirine</b>
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
<b>IBA</b>	<b>ibalizumab</b>
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 <sub>0-12h</sub>	area under the curve at 12 hours post-dose
AUC <sub>24h</sub>	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 <sub>0h</sub>	pre-dose concentration
C <sub>12</sub> or C <sub>12h</sub>	mid-dose concentration
CBC	complete blood count
CD4	CD4 T lymphocyte
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CK	creatinine kinase
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	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

<b>Acronym</b>	<b>Term</b>
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
<b>NTD</b>	<b>neural tube defect</b>
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	<i>Pneumocystis jirovecii</i> 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 <sub>1/2</sub>	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 <sub>max</sub>	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<sub>10</sub> HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

Age	CD4 Percentage				Log <sub>10</sub> HIV RNA Copy Number		
	10%	20%	25%	30%	6.0	5.0	4.0
<b>Percent Mortality (95% Confidence Interval)</b>							
<b>6 Months</b>	28.7	12.4	8.5	6.4	9.7	4.1	2.7
<b>1 Year</b>	19.5	6.8	4.5	3.3	8.8	3.1	1.7
<b>2 Years</b>	11.7	3.1	2.0	1.5	8.2	2.5	1.1
<b>5 Years</b>	4.9	0.9	0.6	0.5	7.8	2.1	0.7
<b>10 Years</b>	2.1	0.3	0.2	0.2	7.7	2.0	0.6
<b>Percent Developing AIDS (95% Confidence Interval)</b>							
<b>6 Months</b>	51.4	31.2	24.9	20.5	23.7	13.6	10.9
<b>1 Year</b>	40.5	20.9	15.9	12.8	20.9	10.5	7.8
<b>2 Years</b>	28.6	12.0	8.8	7.2	18.8	8.1	5.3
<b>5 Years</b>	14.7	4.7	3.7	3.1	17.0	6.0	3.2
<b>10 Years</b>	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)**

Age (Years)	Absolute CD4 Cell Count (cells/mm <sup>3</sup> )					
	<50	50–99	100–199	200–349	350–499	500+
<b>Rate of Death Per 100 Patient-Years</b>						
<b>0–4</b>	59.3	39.6	25.4	11.1	10.0	3.5
<b>5–14</b>	28.9	11.8	4.3	0.89	0.00	0.00
<b>15–24</b>	34.7	6.1	1.1	0.71	0.58	0.65
<b>25–34</b>	47.7	10.8	3.7	1.1	0.38	0.22
<b>35–44</b>	58.8	15.6	4.5	0.92	0.74	0.85
<b>45–54</b>	66.0	18.8	7.7	1.8	1.3	0.86
<b>55+</b>	91.3	21.4	17.6	3.8	2.5	0.91
<b>Rate of AIDS or Death per 100 Patient-Years</b>						
<b>0–4</b>	82.4	83.2	57.3	21.4	20.7	14.5
<b>5–14</b>	64.3	19.6	16.0	6.1	4.4	3.5
<b>15–24</b>	61.7	30.2	5.9	2.6	1.8	1.2
<b>25–34</b>	93.2	57.6	19.3	6.1	2.3	1.1
<b>35–44</b>	88.1	58.7	25.5	6.6	4.0	1.9
<b>45–54</b>	129.1	56.2	24.7	7.7	3.1	2.7
<b>55+</b>	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<sup>a</sup>**

Baseline HIV RNA <sup>c</sup> (Copies/mL) Baseline CD4 Percentage	No. Patients <sup>d</sup>	Deaths <sup>b</sup>	
		Number	Percentage
<b>≤100,000</b>			
≥15%	103	15	(15%)
<15%	24	15	(63%)
<b>&gt;100,000</b>			
≥15%	89	32	(36%)
<15%	36	29	(81%)

<sup>a</sup> Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

<sup>b</sup> Mean follow-up: 5.1 years.

<sup>c</sup> Tested by NASBA<sup>®</sup> assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

<sup>d</sup> 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**

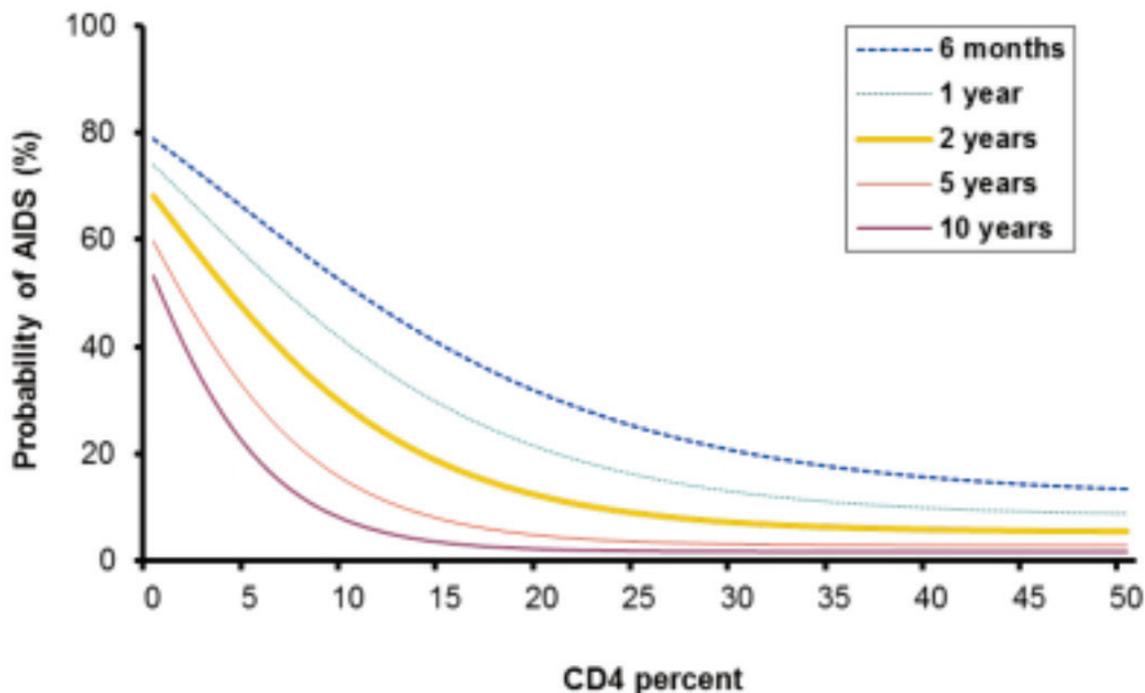


Figure modified from *Lancet* 2003;362:1605-1611

**Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

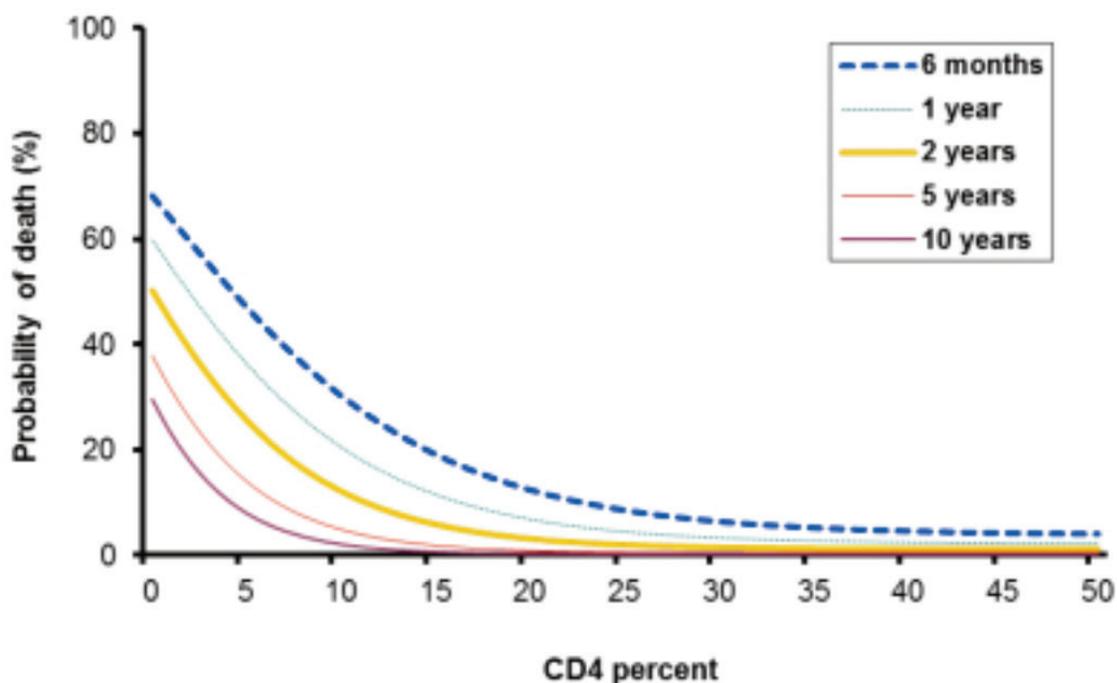


Figure modified from *Lancet* 2003;362:1605-1611

**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\***

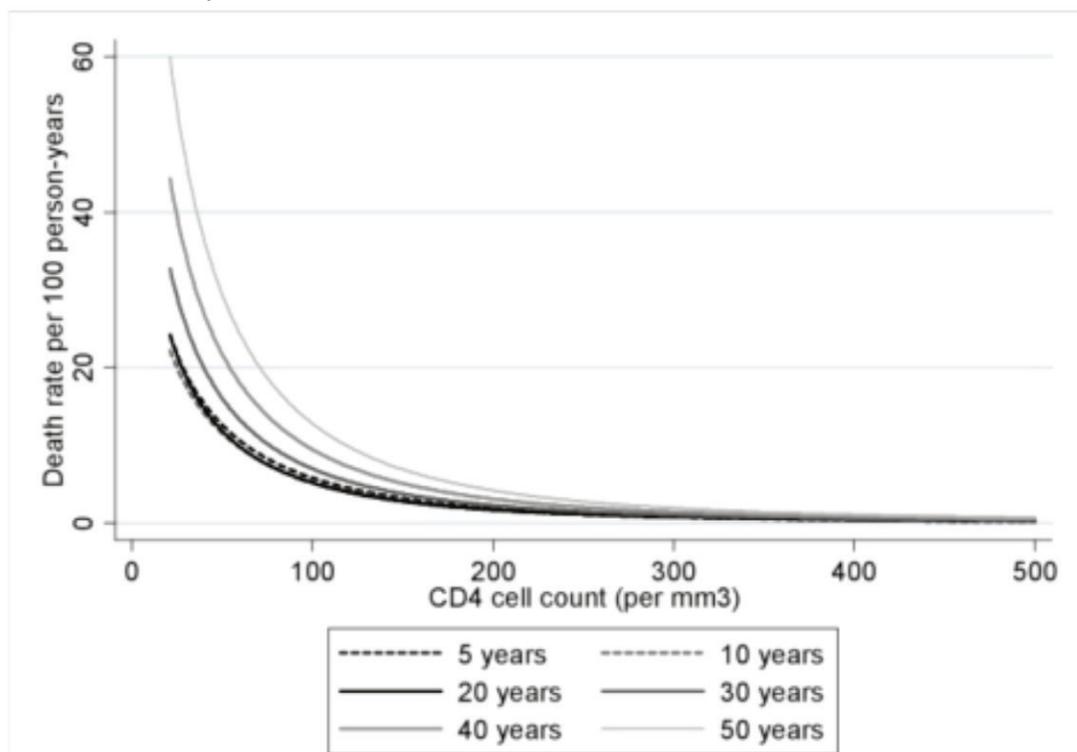


Figure modified from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis.* 2008;197:398-404.

**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**

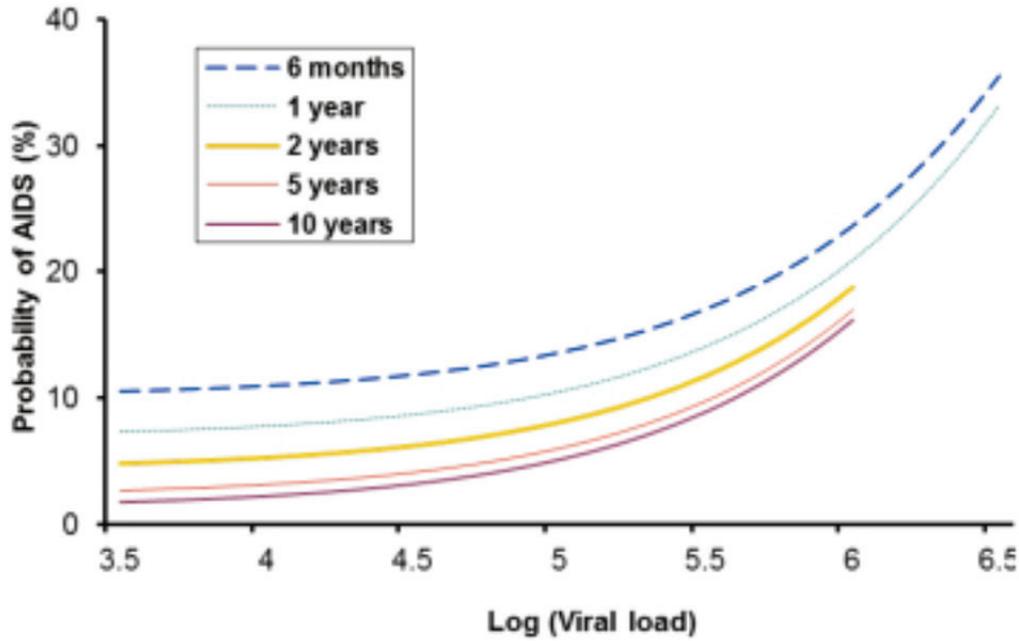


Figure modified from *Lancet* 2003;362:1605-1611

**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**

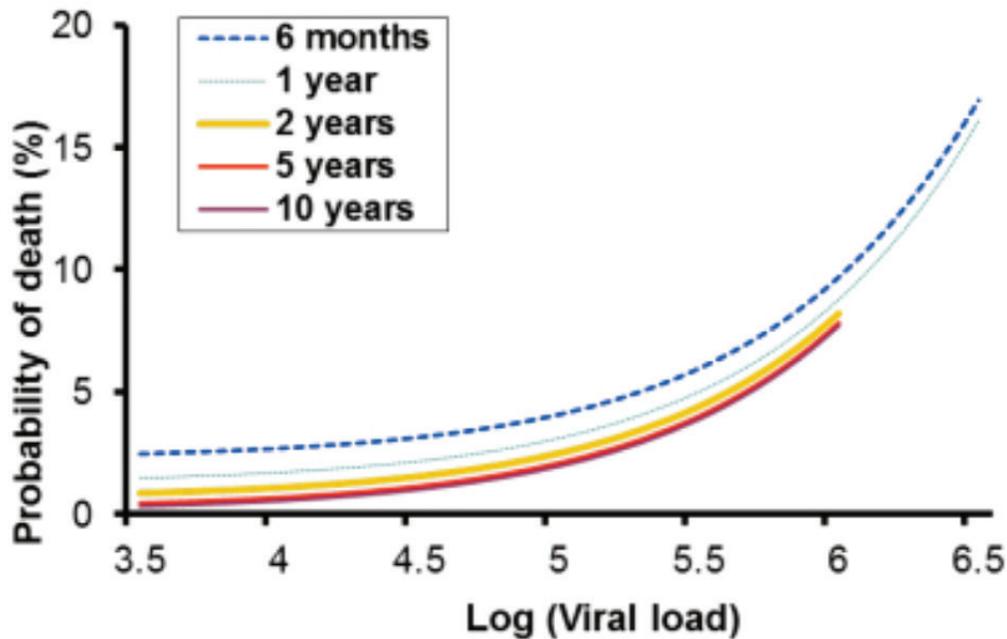


Figure modified from *Lancet* 2003;362:1605-1611