



## **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 May 22, 2018; last reviewed May 22, 2018)

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

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

### May 22, 2018

The Panel updated the text and references of the April 2017 Pediatric Guidelines to include new data and publications. Key updates are summarized below.

#### Introduction

- The Panel has described the process of coordinating with the authors of the [Perinatal Guidelines](#) to jointly develop three sections of the Pediatric Guidelines that are shared with the [Perinatal Guidelines](#).
- Contact information for the [Clinician Consultation Center](#) has been added to facilitate access to expert consultation by phone when needed. The Clinical Consultation Center can be contacted at (800) 933-3413, 9 a.m. to 8 p.m. EST, Monday through Friday.

#### Clinical and Laboratory Monitoring of Pediatric HIV Infection

- The list of bulleted recommendations has been updated to recommend the use of viral load measurements every 3 to 4 months to monitor antiretroviral therapy (ART) adherence and disease progression (**AIII**).

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

- The Panel has increased the strength of its recommendations for initiating ART in children aged  $\geq 1$  year who are asymptomatic or who have mild symptoms and who have CD4 T lymphocyte (CD4) cell counts  $\geq 1,000$  cells/mm<sup>3</sup> (for those aged 1–6 years) or CD4 cell counts  $\geq 500$  cells/mm<sup>3</sup> (for those aged  $\geq 6$  years); ratings were changed from Moderate (**BI\***) to Strong (**AI\***). Thus, the Panel now recommends that **all** children receive ART, regardless of symptoms or CD4 count.

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

- The Panel's bulleted recommendation about individualizing initial antiretroviral (ARV) regimens was revised to include the following additional factors for clinicians to consider when choosing an ARV regimen: drug efficacy, potential adverse effects, and patient and family preferences.
- [Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children](#) and the associated text were revised to reflect updated Panel recommendations. An additional column and footnotes indicating whether drugs are available in fixed-dose combination (FDC) formulations were added to the Table. Additional information is available about drug formulations in [Appendix A: Pediatric Antiretroviral Drug Information](#). Updated recommendations are summarized below.
  - The Panel now recommends raltegravir as a *Preferred* INSTI regimen from birth to age 6 years. This change adds a *Preferred* regimen to the limited options available for children aged  $<2$  years. However, the Panel acknowledges that data in this age group are limited and that neonatal dosing and administration of raltegravir granules for oral suspension can be challenging.

- Genvoya, an FDC tablet that contains elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF), is now an *Alternative* regimen for children aged  $\geq 6$  years to  $< 12$  years and weighing  $\geq 25$  kg. Genvoya continues to be a *Preferred* regimen for patients aged  $\geq 12$  years and weighing  $\geq 35$  kg who are not sexually mature (i.e., those who have a sexual maturity rating [SMR] 1–3).
- TAF used in combination with emtricitabine is now a *Preferred* nucleoside reverse transcriptase inhibitor (NRTI) backbone option for children and adolescents aged  $\geq 6$  years who are not sexually mature (SMR 1–3). TAF was previously a *Preferred* option only for those aged  $\geq 12$  years.
- Tenofovir disoproxil fumarate (TDF) used in combination with lamivudine or emtricitabine is now recommended as an *Alternative* NRTI backbone option for children aged  $\geq 2$  years to 12 years; the potential risks of decreased bone mineral density should be weighed against the benefits of therapy. These options were previously recommended for use in *Special Circumstances* in children aged  $\geq 2$  years with SMR of 1 or 2.
- Zidovudine used in combination with lamivudine or emtricitabine was changed from a *Preferred* to an *Alternative* NRTI backbone for children and adolescents aged  $\geq 6$  to years who are not sexually mature (SMR 1–3).

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

- The Panel has updated its recommendations to indicate that didanosine or stavudine **should never be used** as part of an ARV regimen, due to the significant toxicities of these drugs and the availability of safer agents.
- [Table 9. Antiretroviral Regimens or Components Not Recommended for Initial Treatment of HIV Infection in Children](#) and [Table 10. ART Regimens or Components that Should Never Be Recommended for Treatment of HIV Infection in Children](#) have been updated accordingly.

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

- In [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#), the Panel has updated [Table 16. Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimens](#).
- [Considerations about Interruptions in Antiretroviral Therapy](#) now includes issues that may contribute to interrupted ART in children from limited resource settings, including the need to plan for potential interruptions (e.g., extended travel).

### **Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection**

- The section on therapeutic drug monitoring has been removed, but it is available in the [archive of previous versions of the Pediatric Guidelines](#).

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

Drug sections in this appendix were reviewed and updated to include new pediatric data and dosing and safety information, plus new formulations and FDCs. Significant changes are summarized below:

- The [Emtricitabine](#) and [Tenofovir Alafenamide](#) sections have been updated with new pediatric dosing for Descovy, the FDC of emtricitabine/TAF (FTC/TAF). FTC/TAF is approved for use in children weighing  $\geq 25$  kg. There are insufficient data to recommend the use of FTC/TAF in combination with a boosted protease inhibitor (PI) in children weighing  $< 35$  kg. For children and adolescents weighing  $\geq 35$  kg, FTC/TAF can be used in combination with a non-nucleoside reverse transcriptase inhibitor, an integrase strand transfer inhibitor (INSTI), or a boosted PI.

- The [Lamivudine](#) section was updated with new Food and Drug Administration (FDA) pediatric dosing recommendations for children aged  $\geq 3$  months to address the pharmacokinetic fluctuations that occur when sorbitol is given. However, because of the lack of clinical experience with starting once-daily lamivudine at the higher dose, the Panel continues to recommend a change from twice-daily to once-daily dosing of lamivudine (solution or tablets) only in children who are aged  $\geq 3$  years and who have been stable on a twice-daily regimen for  $\geq 36$  weeks.
- The [Efavirenz](#) section now includes information about using opened capsules as a sprinkle preparation for children who are unable to swallow capsules. Information was also added about Symfi Lo, a new FDC that contains efavirenz/lamivudine/TDF and that has been FDA-approved for children weighing  $\geq 35$  kg and adults. However, the Panel has not yet discussed or made recommendations about this formulation, which contains a lower dose of efavirenz (400 mg). Use of Symfi Lo will be addressed in a later update.
- The [Atazanavir](#) section now includes once-daily dosing of atazanavir capsules for children aged  $\geq 6$  years and weighing  $\geq 15$  kg, in accordance with new FDA recommendations.
- The [Ritonavir](#) section has been updated with information about a new pediatric oral powder formulation that can be administered in 100-mg increments.
- [Bictegravir](#), a new INSTI, was added to the drug appendix. Bictegravir (BIC) is available only as Biktarvy, an FDC that contains BIC/FTC/TAF and is FDA-approved for use in adults. Although not yet approved for pediatric use, the adult dose of bictegravir is being studied in children and adolescents aged 12 years to 18 years and weighing  $\geq 35$  kg.
- [Elvitegravir](#) tablets have been discontinued by the manufacturer; the drug is only available in FDC formulations.
- The [Elvitegravir](#), [Cobicistat](#), [Emtricitabine](#), and [Tenofovir Alafenamide](#) sections were updated to reflect the recent FDA approval of Genvoya, an FDC that contains these drugs, for use in children and adolescents weighing  $\geq 25$  kg with any SMR. This FDC was previously approved only for use in adolescents weighing  $\geq 35$  kg. Genvoya can be used in ART-naive patients or to replace the current ARV regimen in patients who are virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) and who have been on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.
- The [Raltegravir](#) section was updated with new information about the neonatal dosing of raltegravir granules for oral suspension and the new film-coated poloxamer HD tablet.
  - Raltegravir granules for oral suspension are now FDA-approved and recommended by the Panel for use in neonates aged  $\geq 37$  weeks of gestation and weighing  $\geq 2$  kg. The updated instructions for preparing the suspension result in a final concentration of 10 mg/mL, rather than 20 mg/mL. This change is reflected in the new neonatal dosing table and updates to the dosing table for children aged  $\geq 4$  weeks and weighing  $\geq 3$  kg to  $< 20$  kg.
  - The Panel recommends once-daily raltegravir HD for use in children and adolescents weighing  $\geq 50$  kg who are ART-naive or virologically suppressed on an initial regimen of twice-daily raltegravir tablets. The FDA approval of raltegravir HD for use in children and adolescents weighing  $\geq 40$  kg is based on modeling; this formulation has not been studied in children or adolescents.

## November 15, 2017

To facilitate access to relevant content, the guidelines now include three sections that will also appear in the *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States*: [Maternal HIV Testing and](#)

[Identification of Perinatal HIV Exposure](#), [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV Infection](#), and [Diagnosis of HIV Infection in Infants and Children](#).

### **Maternal HIV Testing and Identification of Perinatal HIV Exposure**

- The section has been renamed with revisions to align content in the Pediatric and Perinatal Guidelines regarding maternal HIV testing for prevention on perinatal HIV transmission and identification of perinatal HIV exposure in infants and children.

### **Diagnosis of HIV Infection in Infants and Children**

- This section was updated and reorganized to present content about the timing of diagnostic testing for infants and children prior to detailed information about the specific virologic assays used for diagnosis.

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

- The Panel has added a new section, shared with the [Perinatal Guidelines](#), that details recommendations on ARV management of infants born to women with HIV. This section, formerly titled Infant Antiretroviral Prophylaxis in the Perinatal Guidelines, has been updated to reflect emerging issues in the antiretroviral management of infants born to women with HIV and also incorporates content from Specific Issues in Antiretroviral Therapy for Neonates in previous versions of the Pediatric Guidelines.
- The Panel recommends that the selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission. The uses of ARV regimens in newborns include:
  - ARV prophylaxis – the administration of one or more ARVs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition
  - Empiric HIV therapy – the administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later confirmed to be HIV-infected but also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process or during breastfeeding and who do not become infected with HIV
  - HIV therapy – the administration of three-drug combination ARVs at treatment dosages (ART) to newborns with confirmed HIV infection (see [Diagnosis of HIV Infection](#)).
- The Panel recommends combination ARV prophylaxis or empiric HIV therapy for newborns at higher risk of HIV acquisition and HIV therapy for newborns with confirmed HIV infection.
- [Table 11. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn](#) has been added to provide an overview and guidance about antiretroviral management for different clinical categories.
- [Table 12. Newborn ARV Dosing Recommendations](#) has been revised in accordance with updated Panel recommendations for newborn antiretroviral management.

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## Members of Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (Last updated May 22, 2018; last reviewed May 22, 2018)

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).

Panel Chair	
Peter L. Havens, MS, MD	Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee, WI

Panel Vice Chairs	
Ann J. Melvin, MD, MPH	Seattle Children's Hospital, University of Washington, Seattle, WA
Mary E. Paul, MD	Baylor College of Medicine, Houston, TX
Theodore D. Ruel, MD	University of California–San Francisco, San Francisco, CA

Panel Executive Secretary	
Rohan Hazra, MD	National Institutes of Health, Bethesda, MD

Members of the Panel	
Elaine J. Abrams, MD	Columbia University, New York, NY
Lisa Abuogi, MD	University of Colorado, Denver, CO
Allison L. Agwu, MD, SCM (membership ended March 2018)	Johns Hopkins School of Medicine, Baltimore, MD
Ben Banks, MPH, BSW	Ashland, VA
Edmund V. Capparelli, PharmD (membership ended November 2017)	University of California–San Diego, La Jolla, CA
Ellen G. Chadwick, MD	Feinberg School of Medicine–Northwestern University, Chicago, IL
Rana Chakraborty, MD, MS, PhD	Emory University School of Medicine, Atlanta, GA
Diana F. Clarke, PharmD	Boston Medical Center, Boston, MA
Patricia M. Flynn, MD	St. Jude Children's Research Hospital, Memphis, TN
Marc D. Foca, MD	Columbia University, New York, NY
Paul A. Krogstad, MD	University of California–Los Angeles, Los Angeles, CA
Linda Lewis, MD	Clinton Health Access Initiative, Boston, MA
James B. McAuley, MD, MPH, DTM&H	Rush University Medical Center, Chicago, IL
Lynne M. Mofenson, MD	Elizabeth Glaser Pediatric AIDS Foundation, Washington DC
Mark Mirochnick, MD	Boston University School of Medicine, Boston, MA
Paul Palumbo, MD	Geisel School of Medicine at Dartmouth, Lebanon, NH
Vicki B. Peters, MD	New York City Department of Health and Mental Hygiene, New York, NY
Murli Purswani, MD	Bronx-Lebanon Hospital Center, Bronx, NY
Natella Rakhmanina, MD, PhD	Children's National Medical Center, Washington, DC
Leslie Raneri, MSSW, MPH, LCSW	Texas Children's Hospital West Campus, Houston, TX

## Members of Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (Last updated May 22, 2018; last reviewed May 22, 2018)

<b>Members of the Panel, continued</b>	
Richard M. Rutstein, MD	Children's Hospital of Philadelphia, Philadelphia, PA
Dorothy Shaw, BA (membership ended November 2017)	Birmingham, AL
Russell Van Dyke, MD	Tulane University School of Medicine, New Orleans, LA
Geoffrey A. Weinberg, MD	University of Rochester School of Medicine and Dentistry, Rochester, NY

<b>Members from the Department of Health and Human Services</b>	
Yodit Belew, MD	Food and Drug Administration, Silver Spring, MD
Mindy Golatt, MPH, MA, RN, CPNP	Health Resources and Services Administration, Rockville, MD
Patrick Jean-Philippe, MD	National Institutes of Health, Bethesda, MD
Steve Nesheim, MD	Centers for Disease Control and Prevention, Atlanta, GA
George K. Siberry, MD, MPH	National Institutes of Health, Bethesda, MD

<b>Non-Voting Observers</b>	
Jason Brophy, MD, MSc, DTM&H	Children's Hospital of Eastern Ontario, Ottawa ON
Deborah Storm, MSN, PhD	Fairfield, CA. Formerly, François-Xavier Bagnoud Center, Rutgers School of Nursing, Rutgers, The State University of New Jersey, Newark, NJ, retired November 1, 2016.

## HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV Financial Disclosure **(Last updated May 22, 2018; last reviewed May 22, 2018)**

Name	Panel Status	Company	Relationship
Abrams, Elaine J.	M	ViiV Advisory Board	Advisory Board Member
Abuogi, Lisa	M	None	N/A
Agwu, Allison L. (membership ended March 2018)	M	Gilead	Scientific Advisory Board Member
Banks, Ben	M	None	N/A
Belew, Yodit	M	None	N/A
Brophy, Jason	NVO	Abbott Labs	Research Support
Capparelli, Edmund V. (membership ended November 2017)	M	<ul style="list-style-type: none"> <li>• Atox Bio</li> <li>• Celltrion</li> <li>• Cemptra</li> <li>• Ironshore</li> <li>• Patara</li> <li>• The Medicines Company</li> </ul>	<ul style="list-style-type: none"> <li>• Consultant</li> <li>• Consultant</li> <li>• DSMB Member</li> <li>• Consultant</li> <li>• Consultant</li> <li>• DSMB Member</li> </ul>
Chadwick, Ellen G.	M	AbbVie/Abbott Labs	Stockholder
Chakraborty, Rana	M	<ul style="list-style-type: none"> <li>• Merck</li> <li>• ViiV</li> </ul>	<ul style="list-style-type: none"> <li>• Travel Support, Consultant</li> <li>• Advisory Board</li> </ul>
Clarke, Diana F.	M	None	N/A
Flynn, Patricia M.	M	Merck	Consultant
Foca, Marc D.	M	None	N/A
Golatt, Mindy	HHS	None	N/A
Havens, Peter L.	C	None	N/A
Hazra, Rohan	ES	None	N/A
Jean-Philippe, Patrick	HHS	None	N/A
Krogstad, Paul A.	M	Johnson & Johnson	Spouse holds stock
Lewis, Linda	M	None	N/A
McAuley, James B.	M	None	N/A
Melvin, Ann J.	VC	Merck	Research Support
Mirochnick, Mark	M	<ul style="list-style-type: none"> <li>• Merck</li> <li>• ViiV</li> </ul>	<ul style="list-style-type: none"> <li>• DSMB Member, Research Support</li> <li>• DSMB Member, Consultant</li> </ul>
Mofenson, Lynne M.	M	None	N/A
Nesheim, Steve	M	None	N/A
Palumbo, Paul	M	<ul style="list-style-type: none"> <li>• Gilead</li> <li>• Janssen Pharmaceuticals</li> </ul>	<ul style="list-style-type: none"> <li>• DSMB Member</li> <li>• DSMB Member</li> </ul>
Paul, Mary E.	VC	None	N/A
Peters, Vicki B.	M	None	N/A
Purswani, Murli	M	None	N/A
Rakhmanina, Natella	M	<ul style="list-style-type: none"> <li>• Pfizer</li> <li>• Gilead</li> </ul>	<ul style="list-style-type: none"> <li>• Research Support</li> <li>• Research Support</li> </ul>

## HHS Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV Financial Disclosure **(Last updated May 22, 2018; last reviewed May 22, 2018)**

Name	Panel Status	Company	Relationship
Raneri, Leslie	M	None	N/A
Ruel, Theodore D.	VC	None	N/A
Rutstein, Richard M.	M	None	N/A
Shaw, Dorothy (membership ended November 2017)	M	None	N/A
Siberry, George K.	HHS	None	N/A
Storm, Deborah	NVO	<ul style="list-style-type: none"> <li>• Eli Lilly and Company</li> <li>• Merck</li> <li>• Roche</li> </ul>	<ul style="list-style-type: none"> <li>• Stockholder</li> <li>• Stockholder</li> <li>• Stockholder and stock options</li> </ul>
Van Dyke, Russell	M	Gilead	Research Support
Weinberg, Geoffrey A.	M	Merck	Research Support

**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 May 22, 2018; last reviewed May 22, 2018)

The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* (Pediatric Guidelines) address the use of antiretroviral therapy (ART) for **children living with HIV, including adolescents** with sexual maturity rating (SMR, formerly Tanner staging) I to III (the guidelines developed by the Panel on [Antiretroviral Guidelines for Adults and Adolescents](#) are suitable for the care and management of **adolescents in late puberty [SMR IV–V]**). Guidance on management of adverse events associated with use of antiretroviral (ARV) drugs in children and a detailed review of information about safety, efficacy, and pharmacokinetics (PK) of ARV agents in children is also included. The Department of Health and Human Services (HHS) Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel), a working group of the Office of AIDS Research Advisory Council (OARAC), reviews new data on an ongoing basis and provides regular updates to the guidelines. The guidelines are available on the *AIDSinfo* website at <http://aidsinfo.nih.gov>.

The *AIDSinfo* website also includes separate guidelines for:

1. The prevention and treatment of opportunistic infections (OIs) in children exposed to HIV and children with HIV infection,<sup>1</sup>
2. The use of ARV agents in adolescents and adults with HIV,<sup>2</sup>
3. The use of ARV drugs in pregnant women with HIV,<sup>3</sup> and
4. 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 at <http://www.who.int/hiv/pub/arv/en>.

**The Pediatric Guidelines and the Perinatal Guidelines contain content that is closely related and sometimes overlapping. 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 the HIV-Exposed Neonate**

Since the guidelines were first developed in 1993 (with the support of the François-Xavier Bagnoud Center, Rutgers, The State University of New Jersey), advances in medical management have dramatically reduced both **the number of new pediatric HIV infections and the morbidity and mortality in children living with HIV in the United States. The widespread use of ARV drugs in pregnant women living with HIV and ARV prophylaxis in HIV-exposed infants have together reduced vertical transmission rates to less than 2%, with fewer than 50 new infant infections estimated for the United States in 2014.**<sup>5</sup> Since the **introduction of combination ART**, mortality in children with perinatal HIV infection has decreased by more than 80% to 90%, and opportunistic and other related infections in children have significantly declined.<sup>6,7</sup> **Children living with HIV are less likely to develop AIDS because of routine and early initiation of effective ART.**<sup>8,9</sup> ARV drug-resistance testing has enhanced the ability to choose effective initial and subsequent regimens. Treatment strategies continue to focus on timely initiation of ART regimens that are capable of maximally suppressing viral replication to prevent disease progression, preserve or restore immunologic function, and prevent the development of drug resistance. In addition, the availability of new drugs and drug formulations has led to more potent regimens with lower toxicity, lower pill burden, and less frequent medication administration—all factors that can improve adherence and outcomes. Finally, as children living



with HIV grow older, there are new challenges related to adherence, drug resistance, reproductive health planning, transition to adult medical care, and the potential for long-term complications from HIV and its treatments.<sup>10-13</sup>

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

- Acquisition of infection through perinatal exposure for most children living with HIV;
- *In utero* and neonatal exposure to ARV drugs in most children with perinatal HIV infection;<sup>14</sup>
- The need to use HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months old;
- Age-specific interpretation of CD4 T lymphocyte (CD4) cell counts;
- Higher plasma viral loads in infants with perinatal HIV infection than in adolescents and adults with **nonperinatal** HIV infection;
- Changes in PK parameters with age, caused by the continuing development and maturation of organ systems involved in drug absorption, distribution, metabolism, and clearance;<sup>15</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 living with HIV is complex and evolves rapidly as results of new research are reported, new ARV drugs are approved, and new approaches to treatment are recommended. As new drugs become available, clinical trials are critically needed to define appropriate drug doses and identify possible toxicities in infants, children, and adolescents. As additional ARV drugs become approved and optimal strategies for use of these drugs in children become better understood, the Panel will modify these guidelines. The recommendations in these guidelines are based on the current state of knowledge regarding the use of ARV drugs in children. Evidence is drawn primarily from published data regarding the treatment of HIV in infants, children, adolescents, and adults; however, when no such data are available, unpublished data and the clinical expertise of the Panel members are also considered. These guidelines are only a starting point for medical decision-making and are not meant to supersede the judgment of clinicians who are experienced in the care of children with HIV infection. Because of the complexity of caring for children living with HIV, and the decreasing number of children with perinatally acquired HIV in the United States, health care providers with limited experience in the care of these patients should consult with a pediatric HIV specialist. **The HIV/AIDS Management Clinician Consultation Center is an excellent resource for phone consultation. They can be contacted at (800) 933-3413, 9 am to 8 pm EST, Monday through Friday.**<sup>16</sup>

## Guidelines Development Process

An outline of the composition of the Panel and the guidelines process can be found in Table 1.

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

Topic	Comment
<b>Goal of the Guidelines</b>	Provide guidance to HIV care practitioners on the optimal use of ARV agents in infants, children, and adolescents (through mid-puberty) living with HIV in the United States.
<b>Panel Members</b>	The Panel is composed of approximately 35 voting members who have expertise in management of HIV infection in infants, children, and adolescents. Members include representatives from the Committee on Pediatric AIDS of the American Academy of Pediatrics and community representatives with knowledge of pediatric HIV infection (e.g., parents and caregivers of children and youth living with HIV). The Panel also includes at least one representative from each of the following HHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). A representative from the Canadian Pediatric AIDS Research Group participates as a nonvoting, <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 for management of HIV infections. A list of the latest disclosures is available on the <i>AIDSinfo</i> website ( <a href="http://aidsinfo.nih.gov">http://aidsinfo.nih.gov</a> ).
<b>Users of the Guidelines</b>	Providers of care to infants, children, and adolescents living 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 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 section working groups. The recommendations are generally based on studies published in peer-reviewed journals. The Panel may occasionally use unpublished data to revise the guidelines, particularly when the new information relates to dosing or patient safety. These data come from presentations at major conferences or from the FDA and/or drug manufacturers.
<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 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>	<p>These guidelines focus on infants, children, and adolescents in early puberty (SMR I–III) living with HIV. Guidance for treatment of adolescents in late puberty (SMR IV–V) is provided by the <a href="#">Panel on Antiretroviral Guidelines for Adults and Adolescents</a>.</p> <p>Separate guidelines outline the use of ART in pregnant women with HIV infection (including maternal and infant interventions for prevention of perinatal transmission), <a href="#">ART for nonpregnant adults and postpubertal adolescents with HIV infection</a>, and <a href="#">ARV prophylaxis</a> for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the <i>AIDSinfo</i> website (<a href="http://www.aidsinfo.nih.gov">http://www.aidsinfo.nih.gov</a>).</p>
<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 significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the <i>AIDSinfo</i> website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed, with updates as appropriate, at least once a year.
<b>Public Comments</b>	A 2-week public comment period follows release of the updated guidelines on the <i>AIDSinfo</i> website. The Panel reviews comments received 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@aidsinfo.nih.gov">contactus@aidsinfo.nih.gov</a> .

## ***Basis for Recommendations***

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

Because licensure of drugs in children often is based on extrapolation of efficacy data from adult trials in addition to safety and PK data from studies in children, recommendations for ARV drugs 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 PKs of the drug in children, indicating that systemic exposure in adults and children are similar; and
- Studies are provided that support the safety of the drug in pediatric patients.<sup>17-19</sup>

Studies relating drug activity to drug levels (pharmacodynamic data) in children also should be available if there is a concern that concentration-response relationships might be different in children. In many cases, there is much more substantial and higher-quality evidence related to use of ARV drugs from studies (especially randomized clinical trials) in adults than from studies in children. Therefore, for pediatric recommendations, the following rationale has been used when the evidence from studies in children is limited **or of lower quality**:

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

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

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

- The criteria do not differ for adults and children.

In an effort to increase the amount and improve the quality of evidence available for guiding management of HIV infection in children, the discussion of available trials with children and their caregivers is encouraged. Information about clinical trials for adults and children with HIV infection can be obtained from the

AIDSinfo website (<https://aidsinfo.nih.gov/Clinical-Trials/>) or by telephone at (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 <u>in children</u> <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 <u>in adults</u> , with clinical outcomes and/or validated laboratory endpoints plus accompanying data <u>in children</u> <sup>a</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
<b>C:</b> Optional recommendation for the statement	<b>II:</b> One or more well-designed, nonrandomized trials or observational cohort studies <u>in children</u> <sup>a</sup> with long-term clinical outcomes
	<b>II*:</b> One or more well-designed, nonrandomized trials or observational cohort studies <u>in adults</u> with long-term clinical outcomes plus accompanying data <u>in children</u> <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> Studies that include children or children and adolescents, but not studies limited to post-pubertal adolescents

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# Maternal HIV Testing and Identification of Perinatal HIV Exposure (Last updated November 15, 2017; last reviewed November 15, 2017)

## 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 HIV-negative women in the United States should be tested as early as possible during each pregnancy **(AII)**.
- Repeat HIV testing in the third trimester is recommended for pregnant women with initial negative HIV antibody tests who are known to be at risk of acquiring HIV, who are receiving care in facilities that have an HIV incidence in pregnant women of at least 1 per 1,000 per year, who are incarcerated, or who reside in jurisdictions with elevated HIV incidence (see [Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings](#) and <http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf>) **(AII)**.
- Expedited HIV testing at the time of labor or delivery should be performed for any woman with undocumented HIV status; testing should be available 24 hours a day, and results available within 1 hour **(AII)**. If results are positive, intrapartum and infant postnatal antiretroviral (ARV) drug prophylaxis should be initiated immediately, pending results of supplemental HIV testing **(AII)** see [Perinatal Guidelines](#) for guidance.
- Women who have not been tested for HIV before or during labor should undergo expedited HIV antibody testing during the immediate postpartum period (or their newborns should undergo expedited HIV antibody testing) **(AII)**. If results in mother or infant are positive, an appropriate infant antiretroviral (ARV) drug regimen should be initiated immediately, and the mothers should not breastfeed unless supplemental HIV testing is negative **(AII)**. Infants with initial positive HIV viral tests (RNA, DNA) should have their ARV regimen modified, if necessary, to a three-drug combination of ARV drugs at treatment dosages (antiretroviral therapy) (see [Antiretroviral Management of Exposed Infants](#)) **(AII)**.
- Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.
- HIV testing to determine HIV status is recommended for infants and children in foster care and adoptees for whom maternal HIV status is unknown **(AIII)**.

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

**Rating of Evidence:** I = One or more randomized trials in children<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 Care in the Perinatal Guidelines](#)) or as early in pregnancy as possible. This provides the best opportunity to prevent infant acquisition of HIV, and to identify 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 (the Panel), 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 consistent with state and local laws (<http://ncccf.ucsf.edu/clinical-resources/hiv-aids-resources/state-hiv-testing-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. The “opt-out” approach during pregnancy is allowed in every jurisdiction. The “opt-in” approach involves obtaining specific consent before testing and has been associated with lower testing rates.<sup>6,7</sup> The mandatory newborn HIV testing approach, adopted by several states, involves testing of newborns for perinatal HIV exposure with or without maternal consent, if prenatal or intrapartum maternal testing is not performed.

Knowledge of antenatal maternal HIV status enables:

- Women living with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections for their own health.
- **Initiation of treatment in the identified women**, which may also decrease risk of transmission to their partners.<sup>2,8,9</sup>
- Provision of ART to the mother during pregnancy and labor, and antiretroviral (ARV) drug prophylaxis to the newborn to reduce the risk of perinatal transmission of HIV;
- Counseling of women living with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce perinatal transmission of HIV;<sup>10-12</sup>
- Counseling of women living with HIV about the risks of HIV transmission through breast milk (breastfeeding is not recommended for women with HIV living in the United States);<sup>13</sup>
- Initiation of prophylaxis against *Pneumocystis jirovecii* pneumonia beginning at age 4 to 6 weeks in all infants with HIV and in those infants exposed to HIV whose HIV status remains indeterminate;<sup>14</sup> and
- Early diagnostic evaluation of infants exposed to HIV, (**see Diagnosis section**) as well as testing of partners and other children, to permit prompt initiation of ART in individuals with HIV.<sup>1,15,16</sup>

Technological improvements have resulted in increased sensitivity to early HIV acquisition and reduced performance time for laboratory-based assays, allowing completion in less than 1 hour. Accordingly, the Panel now incorporates CDC's 2014 HIV Laboratory Testing Recommendations.<sup>17</sup> The guidelines recommend that HIV testing begin with an immunoassay capable of detecting HIV-1 antibodies and HIV-1 p24 antigen (referred to as an antigen/antibody combination immunoassay, **or a fourth-generation HIV antigen/antibody assay**). Individuals with a reactive antigen/antibody combination assay should be tested further with an HIV-1/HIV-2 antibody differentiation assay (supplemental testing). Individuals with a reactive antigen/antibody combination immunoassay and a nonreactive differentiation test should be tested with a Food and Drug Administration-approved HIV nucleic acid test (NAT) to establish diagnosis of acute HIV (see <http://www.cdc.gov/hiv/pdf/hivtestingalgorithmrecommendation-final.pdf#page=11>).

The **antigen/antibody combination** immunoassay is the test of choice and can be done quickly (referred to as expedited), but requires trained laboratory staff and therefore may not be available in some hospitals 24 hours a day. If this test is unavailable, then initial testing should be performed by the most sensitive expedited or rapid test available. Every delivery unit needs to have access to an HIV test that can be done rapidly (i.e., in <1 hour) 24 hours a day. If positive, testing for confirmation of HIV should be done as soon as possible (as with all initial positive assays). Because older tests have lower sensitivity in the context of recent acquisition of HIV, testing following the 2014 CDC algorithm should be considered as soon as feasible 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 in the Perinatal Guidelines**)<sup>18</sup> for women who:

- Are receiving health care in a jurisdiction that has a high incidence of HIV or AIDS in women between ages 15 and 45, or who are receiving health care in facilities in which prenatal screening identifies at least 1 pregnant woman with HIV per 1,000 women screened (a list of areas where such screening is recommended is found in the [2006 CDC recommendations](#); a more up-to-date list is forthcoming);
- Are known to be at high risk of acquiring HIV (e.g., those who are injection drug users or partners of injection drug users, exchange sex for money or drugs, are sex partners of individuals with HIV, have had a new or more than one sex partner during the current pregnancy, or have been diagnosed with a new

sexually transmitted disease during pregnancy); or

- Have signs or symptoms of acute HIV.<sup>2,3,19,20</sup>

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester, using an antigen/antibody **combination** immunoassay, as these tests have a higher sensitivity in the setting of acute **HIV-1**, compared to older antibody tests.<sup>17,21</sup> When acute retroviral HIV is suspected during pregnancy, in the intrapartum period, or while breastfeeding, a plasma HIV RNA test should be obtained in conjunction with an antigen/antibody combination immunoassay (**see the Acute and Recent [Early] HIV Infection section in the Adult and Adolescent Guidelines**).

## HIV Testing During Labor in Women with Unknown HIV Status

HIV testing is recommended to screen women in labor whose HIV status is undocumented and to identify 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 and neonatal ARV prophylaxis and in reducing perinatal transmission of HIV (see **Intrapartum Care** in the **Perinatal Guidelines**).<sup>1-4,15</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 diagnosed with HIV and their infants.

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

A positive expedited HIV test result must be followed by a supplemental test.<sup>17</sup> Immediate initiation of ARV drug prophylaxis (**including intravenous intrapartum zidovudine**) for prevention of perinatal transmission of HIV is recommended pending the supplemental result after an initial positive expedited HIV test (see **Intrapartum Management** in the **Perinatal Guidelines**).<sup>1-5,15</sup> No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay.<sup>17</sup>

## HIV Testing During the Postnatal Period

Women who have not been tested for HIV before or during labor should be offered expedited testing during the immediate postpartum period; **if mothers are unavailable for testing**, their newborns should undergo expedited HIV testing.<sup>1,3,15</sup> Maternal testing should be done using **the combination** antigen/antibody immunoassay to screen for established and acute HIV-1; results should be obtained in <1 hour. If acute HIV-1 is a possibility, then a plasma HIV NAT test should be sent as well. Use of expedited HIV assays for prompt identification of infants exposed to HIV is essential because neonatal ARV prophylaxis should be initiated as soon as possible after birth—ideally no more than 6 hours after birth—to be effective for the prevention of perinatal transmission. When an initial HIV test is positive in mother or infant, initiation of infant ARV drug prophylaxis and counseling against initiation of breastfeeding is strongly recommended pending results of supplemental HIV tests to confirm and/or differentiate between HIV-1 and HIV-2 (see **ARV Management of Newborns with Perinatal HIV Exposure**). If supplemental tests are negative and acute HIV is excluded, infant ARV drug prophylaxis can be discontinued. In the absence of ongoing maternal HIV exposure, breastfeeding can be initiated. Mechanisms should be developed to facilitate HIV screening for infants who have been abandoned and are in the custody of the state.

### ***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 adopted from a country where results are not reported in English), HIV testing is indicated to identify HIV in those infants or **children**.<sup>1</sup> **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***

The risk of perinatal transmission of HIV is increased in infants born to [women who have acute HIV](#) during pregnancy or lactation.<sup>18,22-25</sup> The antigen/antibody **combination** immunoassay will detect acute infection more readily than other immunoassays. If acute HIV is suspected, a plasma HIV RNA test should be sent as well. Women with possible acute HIV who are breastfeeding should cease breastfeeding immediately until HIV is confirmed or excluded.<sup>13</sup> Pumping and temporarily discarding breast milk can be recommended and (if HIV infection is excluded), in the absence of ongoing maternal exposure to HIV, breastfeeding can resume. Care of pregnant or breastfeeding women identified with acute or early HIV, and their infants, should follow the recommendations in the [Perinatal Guidelines](#).

## **Other Issues**

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

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## Diagnosis of HIV Infection in Infants and Children (Last updated November 15, 2017; last reviewed November 15, 2017)

### Panel's Recommendations

- Virologic assays (i.e., HIV RNA and HIV DNA nucleic acid tests) that directly detect HIV must be used to diagnose HIV infection in infants and children younger than 18 months with perinatal and postnatal HIV exposure; HIV antibody tests should not be used (AII).
- RNA or DNA polymerase chain reaction (PCR) testing are recommended equally for most patients; RNA PCR is recommended for known maternal non-subtype B virus (AII).
- Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:
  - 14 to 21 days (AII)
  - 1 to 2 months (AII)
  - 4 to 6 months (AII)
- Additional virologic diagnostic testing at birth should be considered for infants at higher risk of perinatal HIV transmission (AIII) and at 2 to 4 weeks after cessation of antiretroviral prophylaxis (BIII).
- A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen (AII).
- Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with 1 obtained at age  $\geq 1$  month and 1 at age  $\geq 4$  months, or 2 negative HIV antibody tests from separate specimens obtained at age  $\geq 6$  months (AII).
- Some experts confirm the absence of HIV infection at 12 to 18 months of age in children with prior negative virologic tests by performing an HIV antibody test to document loss of maternal HIV antibodies (BIII).
- Since children aged 18 to 24 months with perinatal HIV exposure occasionally have residual maternal HIV antibodies, definitive exclusion or confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on an HIV nucleic acid test (AII).
- Diagnostic testing in children with non-perinatal exposure only or children with perinatal exposure aged  $>24$  months relies primarily on the use of HIV antibody (or antigen/antibody) tests; when acute HIV infection is suspected, additional testing with an HIV nucleic acid test may be necessary to diagnose HIV infection (AII).

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

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

**Rating of Evidence:** I = One or more randomized trials in children<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

## Diagnose of HIV Infection in Infants and Children

HIV infection can be definitively diagnosed through use of virologic assays in most non-breastfed infants with HIV exposure by age 1 to 2 months and in virtually all infants with HIV infection 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 infection in infants because of transplacental transfer of maternal antibodies to HIV; therefore, a virologic test must be used.<sup>1,2</sup> Positive virologic tests (i.e., nucleic acid tests [NAT]—a class of tests that includes HIV RNA and DNA polymerase chain reaction [PCR] assays, and related RNA qualitative or quantitative assays) indicate likely HIV infection. The first test result should be confirmed as soon as possible by a repeat virologic test on a

second specimen, because false-positive results can occur with both RNA and DNA assays.<sup>3</sup> For additional information on HIV and RNA assays and diagnosis of Group M non-subtype B and Group O HIV-1 infections and HIV-2 infections, see the [Virologic Assays to Diagnose HIV Infection in Infants Younger Than 18 Months With Perinatal HIV-1 Exposure](#) section and [Other Issues](#) section below.

Antigen/antibody combination immunoassays which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are not recommended for infant diagnosis. The sensitivity of the antigen component in the first months of life is less than that of an HIV NAT, and antibody tests should not be used for diagnosis in infants and children less than 18 months of age.<sup>4-6</sup> Children with perinatal HIV exposure aged 18 to 24 months occasionally have residual maternal HIV antibodies; definitive confirmation of HIV infection in children in this age group who are HIV antibody-positive should be based on a NAT (see [Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations](#)). Diagnosis in children aged >24 months relies primarily on HIV antibody and antigen/antibody tests (see [Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months](#)).<sup>1</sup>

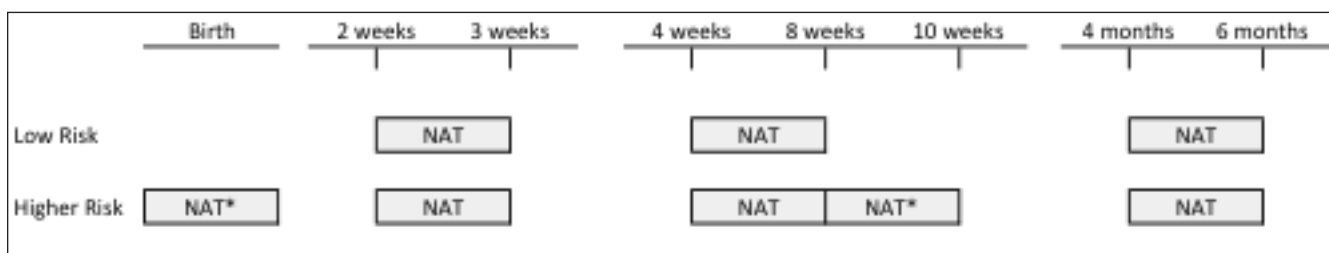
Infants who are found to have positive HIV antibody tests but whose mothers' HIV status is unknown (see [Identification of Perinatal HIV Exposure](#)) should be assumed to be exposed to HIV and undergo HIV diagnostic testing as described below.<sup>7</sup>

For antiretroviral (ARV) management of HIV-exposed and HIV-infected newborns, see the [Antiretroviral Management of Newborns with Perinatal HIV Exposure](#).<sup>8,9</sup>

## Timing of Diagnostic Testing in Infants with Perinatal HIV Exposure

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

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



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

**Higher Risk:** Infants born to mothers living with HIV who did not receive prenatal care, did not receive antepartum or intrapartum ARVs, received intrapartum ARV drugs only, mothers who initiated ART late in pregnancy (late second or third trimester), were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, including those who received combination ARV drugs and did not have sustained viral suppression.

\* For higher-risk infants, additional virologic diagnostic testing should be considered at birth and 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of life).

NAT= nucleic acid test

HIV infection can be **presumptively** excluded in non-breastfed infants with two or more negative virologic tests (one at age  $\geq 14$  days 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 non-breastfed 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 (i.e., no positive virologic test results or low CD4 T lymphocyte [CD4] cell count/percent) or clinical evidence of HIV infection and 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 HIV-uninfected or **presumptively** uninfected.<sup>10</sup> Thus, PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded (see the [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children](#) and [Initial Postnatal Management of the Neonate Exposed to HIV](#) section).

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

Virologic testing at birth should be considered **for newborns at higher risk of perinatal HIV transmission**,<sup>11-16</sup> such as infants born to mothers living 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)**
- Were diagnosed with acute HIV infection during pregnancy
- Had detectable HIV viral load close to the time of delivery
- Received combination ARV drugs and did not have sustained viral suppression

Testing infants exposed to HIV close to the time of birth identifies 20% to 58% of infants with HIV infection; however, in one study that specifically evaluated infants born to mothers who had not received ARV drugs during pregnancy and hence were at higher risk of *in utero* infection, birth testing identified 66.4% of infants with HIV infection.<sup>17</sup> Prompt diagnosis of infant HIV infection is critical to allow for discontinuing ARV prophylaxis and instituting early ART (see [When to Initiate Therapy](#)). Blood samples from the umbilical cord should not be used for diagnostic evaluations because of the potential for contamination with maternal blood. Working definitions have been proposed to differentiate acquisition of HIV infection *in utero* from the intrapartum period. Infants who have a positive virologic test at or before age 48 hours are considered to have early (i.e., intrauterine) infection, whereas infants who have a negative virologic test during the first week of life and subsequent positive tests are considered to have late (i.e., intrapartum) infection.<sup>11,12,18</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 would permit discontinuation of neonatal ARV prophylaxis and initiation of ART (see [Infants Younger than Age 12 Months](#) and Table 5 in [When to Initiate Therapy](#)).

## ***Virologic Testing at Age 1 to 2 Months***

Testing performed at age **1 to 2 months** is intended to maximize the detection of infants with HIV infection.<sup>19,20</sup> Two studies found that although the sensitivity during prophylaxis was not associated with the type of maternal or neonatal ARV prophylaxis, the sensitivity of diagnostic HIV testing during the period of infant ARV prophylaxis was lower compared to the sensitivity during the subsequent testing interval at 3 months of age. Overall, in both studies, 89% of infants with HIV infection were identified by 4 to 6 weeks of age. Of those infants who had negative testing in the first 7 days of life, repeat testing at 4 weeks to 6 weeks of age during the period of neonatal ARV prophylaxis identified 76% of infants with HIV infection in one study,<sup>19</sup> and 68% of infants with HIV infection in the second study.<sup>17</sup> In both studies, infants with negative testing in the first 7 days of life were diagnosed when the next diagnostic test was performed at 3 months of age.

For infants at **higher risk of perinatal HIV transmission**, the Panel suggests an additional virologic test 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of age) given the increased risk of infection and concern that ARV prophylaxis, particularly combination ARV prophylaxis, may reduce the sensitivity of testing during prophylaxis.<sup>7,17,19</sup> In these situations, many experts recommend one test at age 4 to 6 weeks to allow prompt recognition of infected infants, with an additional test at 8 weeks of life (2 weeks after cessation of prophylaxis at 6 weeks of life) to capture additional cases. For infants at low risk of transmission, a single test obtained at 1 to 2 months of age may be timed to occur 2 to 4 weeks after cessation of ARV prophylaxis.

An infant with two negative virologic tests (one at age  $\geq 14$  days and the other at age  $\geq 4$  weeks) or one negative test at age  $\geq 8$  weeks can be viewed as **presumptively** uninfected, assuming the child has not had a positive virologic test, CD4 immunosuppression, or clinical evidence of HIV infection.

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

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

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

Two or more negative HIV antibody tests performed in non-breastfed 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>21,22</sup>

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

Some experts confirm the absence of HIV infection in infants and children with negative virologic tests (when there has not been prior confirmation of two negative antibody tests) by repeat serologic testing between 12 and 18 months of age to confirm that maternal HIV antibodies transferred *in utero* have disappeared.<sup>1</sup> In a recent study, the median age at seroreversion was 13.9 months.<sup>23</sup> Although the majority of infants who are HIV-uninfected will serorevert by age 15 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>23-26</sup>

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

### ***Late Seroreversion ( $\leq 24$ Months of Age)***

Non-breastfed children with HIV exposure with no other HIV transmission risk and no clinical or virologic laboratory evidence of HIV infection may have residual HIV antibodies up to age 24 months (these children are called late seroreverters).<sup>23-26</sup> In one study, 14% of children with HIV exposure who were uninfected seroreverted after age 18 months.<sup>23</sup> These children may have positive immunoassay results but indeterminate supplemental antibody tests (using Western blot or IFA). In such cases, repeat antibody testing at a later time

would document 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 to 24 months.

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

In contrast to late seroreverters, in rare situations postnatal HIV infections have been reported in children with HIV exposure who had prior negative HIV virologic tests. This occurs in children who become infected through an additional risk after completion of testing (see Diagnostic Testing in Children with Non-Perinatal HIV Exposure or Children with Perinatal Exposure Aged >24 Months). If an HIV antibody test is positive at age 18 to 24 months, repeated virologic testing will distinguish residual antibodies in late-seroreverting (uninfected) children from children with antibodies due to true infection.

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

Children with non-subtype B HIV-1 infection and children with HIV-2 infection 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 Non-Perinatal HIV Exposure or Children with Perinatal HIV Exposure Aged >24 Months**

### ***Breastfeeding***

Breastfeeding is a known route of postnatal HIV transmission. Typical scenarios in the United States include women who have not been adequately counseled about infant feeding, women who breastfeed despite being counseled not to (e.g., women from communities where breastfeeding is the norm and women who fear that not breastfeeding would be stigmatizing, including those where avoidance of breastfeeding raise suspicions about maternal HIV infection), and women who learn of their HIV diagnosis only after initiating breastfeeding (e.g., women who were HIV negative during pregnancy but who acquire HIV infection postnatally; breastfeeding during acute HIV infection is associated with an increased risk of perinatal HIV transmission).<sup>30-33</sup> Breast milk from a donor with unrecognized HIV infection at the time of donation is an additional risk factor. Infants who are breastfed by women living with HIV should undergo immediate HIV diagnostic testing, and counseling to discontinue breastfeeding should be provided. Follow-up, age-appropriate testing should be performed at 4 to 6 weeks, 3 months, and 6 months after breastfeeding cessation if the initial tests are negative. Diagnostic testing may be influenced by factors that include the transplacental transfer of maternal antibody resulting in residual antibody in children aged up to 24 months (women who acquired HIV infection before delivery), as well as the possibility of performing the test during acute HIV infection; thus, a NAT would be the choice for initial testing. The receipt of postnatal ARV prophylaxis may delay the detection of HIV infection (see [Antiretroviral Management of Newborns with Perinatal HIV Exposure](#)).<sup>34-36</sup>

### **Premastication**

Receipt of solid food premasticated, prechewed, **or prewarmed** by a caregiver living with HIV has been documented to be associated with risk of HIV transmission.<sup>37-42</sup> If this occurs in children with perinatal HIV exposure aged 24 months or younger with prior negative virologic tests, it will be necessary for such children to undergo virologic diagnostic testing, as they may have residual maternal HIV antibodies (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations).

## Additional Routes of HIV Transmission

Additional routes of HIV transmission in children include sexual abuse or receipt of contaminated blood products. In such cases, maternal HIV status may be negative. If the maternal HIV status is unknown, age-appropriate testing should be performed as described for children with perinatal HIV exposure.

Acquisition of HIV is possible through accidental needlestick injuries, sexual transmission, or injection drug use in older children. Medical procedures performed in settings with inadequate infection control practices may pose a potential risk; although tattooing or body piercing presents a potential risk of HIV transmission, no cases of HIV transmission from these activities have been documented.<sup>43</sup>

## Diagnostic Testing

Diagnosis of HIV-1 infection in infants and children with non-perinatal HIV exposure only or children with perinatal HIV exposure aged >24 months relies primarily on HIV antibody and antigen/antibody tests.<sup>1,44</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 (fourth and fifth generation tests [the fifth generation test differentiates between HIV-1 and HIV-2 antibodies as well as HIV-1 p24 antigen]): Recommended for initial testing to screen for established infection with HIV-1 or HIV-2 and for acute HIV-1 infection (p24 antigen from HIV-1 non-B, non-M and HIV-2 strains may not be detected).<sup>45</sup>
- HIV-1/2 immunoassays (third-generation antibody tests): Alternative for initial testing.
- HIV-1/HIV-2 antibody differentiation immunoassay, which differentiates HIV-1 antibodies from HIV-2 antibodies: Recommended for supplemental testing.
- HIV-1 NAT may be necessary as an additional test to diagnose acute HIV infection.
- HIV-1 Western blot and HIV-1 indirect IFAs (first-generation tests): Alternative for supplemental testing but will not detect acute HIV infection.

Diagnosis of HIV-2 in children with non-perinatal exposure or children with perinatal exposure aged >24 months relies on the Centers for Disease Control and Prevention (CDC)/Association of Public Health Laboratories (APHL) 2014 laboratory testing guidelines, which recommend using an HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies for supplemental testing. This is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test; more than 60% of individuals with HIV-2 infection are misclassified as having HIV-1 by the HIV-1 Western blot.<sup>1,46</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 their public health laboratory or the CDC if an HIV-1/HIV-2 antibody differentiation immunoassay is not conclusive. HIV-2 DNA PCR testing may be necessary for definitive diagnosis (this assay is not commercially available).<sup>47,48</sup>

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

### *HIV RNA Assays*

HIV quantitative RNA assays detect extracellular viral RNA in plasma. Their specificity has been shown to be 100% at birth and at 1, 3, and 6 months of age and is comparable to HIV DNA PCR.<sup>19</sup> HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before being interpreted as documentation of HIV infection in an infant.<sup>49,50</sup> Testing at birth will detect infants who were infected in utero and not those who become infected from exposure during or immediately prior to delivery (i.e., in the intrapartum period). Studies have shown that HIV RNA assays identify 25% to 58% of infants with HIV infection from birth through the first week of life, 89% at age 1 month, and 90% to 100% by age 2 to 3 months (similar to results of HIV DNA PCR for early diagnosis of HIV).<sup>3,7,19,51</sup>



HIV RNA undergoes reverse transcription to double-stranded DNA, which persists intracellularly within an infected cell. HIV DNA PCR assays detect intracellular DNA, and usually remain positive in individuals receiving ARV treatment. In contrast, HIV RNA assays are affected by maternal antenatal treatment or infant combination ARV prophylaxis.<sup>52</sup> In one study, the sensitivity of HIV RNA assays were not associated with the type of maternal or infant ARV prophylaxis, but HIV RNA levels at 1 month were significantly lower in infants with HIV infection receiving multidrug prophylaxis (n = 9) compared to levels among infants receiving single-drug zidovudine prophylaxis (n = 47) (median HIV RNA 2.5 log copies/mL vs. 5.4 log copies/mL, respectively). In contrast, the median HIV RNA levels were high (median HIV RNA 5.6 log copies/mL) by age 3 months in both groups after stopping prophylaxis.<sup>19</sup> Further studies are necessary to evaluate the sensitivity and predictive value of HIV RNA assays during and after receipt of infant ARV prophylaxis.

An HIV quantitative RNA assay can be used as a supplemental test for infants who have an initial positive HIV DNA PCR test. In addition to providing virologic confirmation of infection status, the expense of repeat HIV DNA PCR testing is spared and an HIV RNA measurement is available to assess baseline viral load. This viral load can also be used to determine HIV genotype and guide initial ARV treatment in an infected infant. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting non-subtype B HIV (see Virologic Assays to Diagnose Group M Non-Subtype B and Group O HIV-1 Infections).

The HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) is an alternative diagnostic test that can be used for infant testing. It is the only qualitative RNA test that is FDA-approved.<sup>18,53-56</sup>

### ***HIV DNA PCR And Related Assays***

HIV DNA PCR is a sensitive technique used to detect intracellular HIV viral DNA in peripheral blood mononuclear cells. The specificity of the HIV DNA PCR is 99.8% at birth and 100% at ages 1, 3, 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 that testing at birth will detect infants infected *in utero* and not those infected during the intrapartum period, but the percentage increases to more than 90% by 2 to 4 weeks of age and to 100% at ages 3 months and 6 months.<sup>7,18,19,51</sup>

Two studies provided data on diagnostic testing at different time points in infants with confirmed HIV infection including those who had negative testing at birth (i.e., infants considered to be infected during the intrapartum period). A randomized, international study of 1,684 infants evaluated the efficacy of three different regimens of neonatal prophylaxis containing 6 weeks of zidovudine either alone or with two or three other ARV drugs; none of their 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 (66.4%) of 140 infants with HIV infection were identified at birth, and by 4 to 6 weeks of age, 89% of the 140 infants were identified. Of the 47 infants with HIV infection who had negative DNA PCR tests 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>17</sup> More recent data from Thailand showed that, in non-breastfed infants, receiving an ARV prophylaxis regimen of zidovudine/lamivudine/nevirapine for 6 weeks was associated with a delay in first HIV DNA detection. In this cohort, up to 20% of HIV-exposed infants had their first positive DNA PCR test after 2 months of age, prompting the authors to recommend infant testing at 4 months of age, having discontinued neonatal prophylaxis for at least 4 to 6 weeks.<sup>57</sup>

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

The COBAS AmpliPrep/COBAS TaqMan HIV-1 qualitative test which detects both HIV-1 RNA and proviral DNA in plasma, whole blood, and dried blood spots may be used for infant diagnosis but is not FDA-approved.<sup>58</sup>

## Other Issues

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

Although HIV-1 Group M subtype B is the predominant viral subtype found in the United States, multiple subtypes and recombinant forms are found in the United States with a widespread geographic distribution.<sup>59</sup> In an evaluation of infants with perinatal HIV infection diagnosed in New York state in 2001 and 2002, 16.7% of infants were infected with a non-subtype B strain of HIV, compared with 4.4% of infants born in 1998 and 1999.<sup>60</sup> Among a group of 40 children attending a pediatric HIV clinic in Rhode Island during 1991 through 2012, 14 (35%) were infected with non-B HIV-1 subtypes. All 14 children with non-B subtypes were either born outside the United States or their parents were of foreign origin.<sup>61</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 non-B subtypes formed transmission clusters, including individuals with perinatally-acquired infection.<sup>62</sup> In an analysis of 3,895 HIV-1 sequences collected between July 2011 and June 2012 in the United States, 5.3% were determined to be non-B subtypes (including recombinant forms). Among individual states, the percentage of non-B subtypes ranged from 0% (in 12 states) to 28.6% in South Dakota, with seven states having greater than 10%.<sup>63</sup> 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>64</sup> Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.<sup>65-69</sup> Geographical distribution of HIV groups is available at <http://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp>.

Currently available real-time HIV RNA PCR assays and the qualitative diagnostic RNA assay have improved sensitivity for detection of non-subtype B HIV infection and the less common Group O strains, compared to older RNA assays that did not detect or appropriately amplify many non-B subtypes and Group O HIV<sup>70-75</sup> (see [HIV RNA Monitoring in Children: General Considerations in Clinical and Laboratory Monitoring](#)).

Thus, a real-time PCR assay or qualitative RNA assay, **rather than a DNA PCR assay**, should be used for infant testing when evaluating an infant born to a mother whose HIV infection is linked to an area endemic for non-subtype B HIV or Group O strains, such as Africa or Southeast Asia. Another indication is when initial testing is negative using a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody tests obtained at age  $\geq 6$  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 the CDC may be able to assist in obtaining referrals for diagnostic testing.

### ***Virologic Assays to Diagnose HIV-2 Infections***

HIV-2 infection is endemic in Angola; Mozambique; West African countries, including Cape Verde, Ivory Coast, 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>76-78</sup> It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions.<sup>79,80</sup> HIV-1 and HIV-2 coinfections may also occur, but these are rare outside areas where HIV-2 is endemic. HIV-2 is rare in the United States. Although accurate diagnosis of HIV-2 can be problematic, it is clinically important because HIV-2 strains are resistant to several ARV drugs developed to suppress HIV-1.<sup>81-83</sup>

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 being infected with HIV-2 if her infection is linked to an area endemic for HIV-2 infection or if her HIV testing results are suggestive of HIV-2 infection (i.e., positive initial HIV 1/2 immunoassay test, repeatedly indeterminate results on HIV-1 Western blot, and HIV-1 RNA viral loads at or below the limit of detection; however, the current recommendation to use an HIV-1/HIV-2 antibody differentiation immunoassay for supplemental testing is not subject to the same testing ambiguity as when the HIV-1 Western blot is used as a supplemental test as described below).<sup>1,84</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>47,48</sup> Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.<sup>76,85</sup>

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# Clinical and Laboratory Monitoring of Pediatric HIV Infection

(Last updated May 22, 2018; last reviewed May 22, 2018)

## Panel's Recommendations

- Absolute CD4 T lymphocyte (CD4) cell count and plasma HIV RNA (viral load) should be measured at the time of diagnosis of HIV 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**).
- Antiretroviral (ARV) drug-resistance testing is recommended at the time of HIV diagnosis, before initiation of therapy, in all treatment-naïve patients (**AII**). Genotypic resistance testing is preferred for this purpose (**AIII**).
- After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical adverse effects and to support treatment adherence within 1 to 2 weeks, with laboratory testing for toxicity and viral load response recommended at 2 to 4 weeks after treatment initiation (**AIII**).
- Children on ART should be monitored for therapy adherence, effectiveness, and toxicities routinely (every 3 to 4 months) (**AII\***).
- Additional CD4 cell count and plasma viral load monitoring should be performed for evaluation of children with suspected clinical, immunologic, or virologic deterioration or to confirm an abnormal value (**AIII**). CD4 cell count can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell count values well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years (**AII**). **Viral load measurement every 3 to 4 months is generally recommended to monitor ART adherence and disease progression (AIII).**
- Phenotypic resistance testing should be used (usually in addition to genotypic resistance testing) for patients with known or suspected complex drug resistance mutation patterns, which generally arise after virologic failure of successive ART regimens (**BIII**).
- The absence of detectable resistance to a drug does not ensure that use of the drug will be successful, as mutations may not be detected once the drug has been discontinued. A history of all previously used ARV agents and available resistance test results must be reviewed when making decisions regarding the choice of new agents (**AII**).
- Viral co-receptor (tropism) assays **are recommended** whenever a CCR5 antagonist is being considered **for treatment (AI\*)**. Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist (**AI\***).
- Absolute CD4 cell count is recommended for monitoring immune status in children of all ages, with CD4 percentage as an alternative for children aged <5 years (**AII**).

**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

Laboratory monitoring of children living with HIV poses unique and challenging issues. In particular, normal ranges and the value of CD4 T lymphocyte (CD4) cell count and plasma HIV-1 RNA concentration (viral load) for prediction of risk of disease progression vary significantly by age. This section will address immunologic, virologic, general laboratory, and clinical monitoring of children with HIV, 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 Newly Diagnosed Children

Children who have recently received an HIV diagnosis should have their CD4 cell counts and plasma viral loads measured, and their growth and development evaluated for signs of HIV-associated **abnormalities**. They should also undergo a laboratory evaluation that looks for HIV-associated conditions, including anemia, leukopenia, thrombocytopenia, hypoalbuminemia, nephropathy (urinalysis), and elevated levels of glucose, transaminases, or creatinine. In addition, children with HIV should have a complete age-appropriate medical

history and physical examination (see [Table 3](#)). Opportunistic infection (OI) monitoring should follow guidelines appropriate for the child's exposure history and clinical setting (see the [Pediatric Opportunistic Infections Guidelines](#)).

Laboratory confirmation of HIV infection should be obtained if available documentation is incomplete (see [Diagnosis of HIV Infection](#)). Genotypic resistance testing should be performed, even if ART is not initiated immediately. In addition, a full antiretroviral (ARV) drug history, including exposure to [ARVs for the prevention of perinatal HIV](#) transmission, should be obtained (see [Antiretroviral Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). If abacavir is being considered as part of the regimen, HLA-B\*5701 testing should be sent prior to initiation of that ARV drug, and an alternative ARV drug should be used if HLA-B\*5701 testing is positive (see [Abacavir](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)).<sup>1</sup>

Readiness for ARV drug adherence should be assessed prior to starting ART and associated discussion/counseling implemented.

If a child is not placed on ART after HIV diagnosis, monitoring of CD4 count and plasma viral load should be implemented at least every 3 to 4 months.

### ***Evaluation at Initiation of Combination Antiretroviral Therapy***

At the time of ART initiation, CD4 cell count and plasma viral load should be measured to establish a baseline to monitor ART [response](#). To set the baseline for monitoring ART toxicity (see [Management of Medication Toxicity or Intolerance](#)), complete blood count (CBC) and differential, serum chemistries (including electrolytes, creatinine, glucose, hepatic transaminases), urinalysis, and serum lipids (cholesterol, triglycerides) should be measured. CBC allows monitoring of zidovudine-associated anemia, leukopenia, and macrocytosis (see [Zidovudine](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)). Electrolytes with anion gaps might help identify nucleoside reverse transcriptase inhibitor-associated lactic acidosis. With use of tenofovir disoproxil fumarate (TDF), creatinine may increase, phosphate may decrease, and proteinuria can occur (see [Tenofovir Disoproxil Fumarate](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)). Use of protease inhibitors may be associated with hyperglycemia. Hepatic transaminases (alanine aminotransferase and aspartate aminotransferase) increase with many ARV drugs. Bilirubin should be measured prior to starting atazanavir, because that drug causes an increase in indirect bilirubin (see [Atazanavir](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)). For further details of adverse effects (AEs) associated with a specific ARV drug, see [Tables 15a-15l](#) in [Management of Medication Toxicity or Intolerance](#).

### ***Clinical and Laboratory Monitoring After Initiation of Combination Antiretroviral Therapy (or After a Change in Antiretroviral Therapy)***

Children who start ART or who change to a new regimen should be followed to assess effectiveness, tolerability, and AEs of the regimen and to evaluate medication adherence. Frequent patient visits and intensive follow-up during the initial months after a new ART regimen is started are necessary to support and educate the family. 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 AEs of medications, and both children and their caregivers need assistance to determine whether the effects are temporary and tolerable or 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, non-judgmental manner using layman's terms. This promotes honest reporting and ensures that providers can have a productive dialogue with both children and their caregiver(s), even when medication adherence is reported to be inconsistent.

### ***Within 1 to 2 Weeks of Initiation of Antiretroviral Therapy***

Within 1 to 2 weeks of initiating therapy, children should be evaluated either in person or by phone to identify clinical AEs and to support adherence. Many clinicians plan additional contacts (in person, by

telephone, or via email) with children and caregivers to support adherence during the first few weeks of therapy.

## ***2 to 4 Weeks after Initiation of Antiretroviral Therapy***

Most experts recommend laboratory testing at 2 to 4 weeks (and not more than 8 weeks) after initiation of ART to assess virologic response and laboratory toxicity, though this recommendation is based on limited data. The selection of laboratory chemistry tests is regimen-specific (see above). Plasma viral load monitoring is important as a marker of response to ART because a decline in viral load suggests medication adherence, administration of appropriate doses, and viral drug susceptibility. Some experts favor measuring viral load at 2 weeks to ensure that viral load is declining. A significant decrease in viral load in response to ART should be observed by 4 to 8 weeks of therapy.

## ***Clinical and Laboratory Monitoring for Children Who are Stable on Long-Term Antiretroviral Therapy***

After the initial phase of ART initiation, regimen adherence, effectiveness (CD4 cell count and plasma viral load), and toxicities (history, physical, and laboratory testing as above) should be assessed every 3 to 4 months in children receiving ART. Children who develop symptoms of toxicity should have appropriate laboratory evaluations. If laboratory evidence of toxicity is identified, testing should be performed more frequently until the toxicity resolves.

[Table 3](#) provides one proposed general monitoring schedule, which should be adjusted based on the specific ART regimen a child is receiving.

CD4 count improvement is influenced by the baseline value at 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 cell count and plasma viral load. These studies support less frequent monitoring in stable patients in whom viral suppression has been sustained for at least 1 year.<sup>3-9</sup>

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

- Consistent virus suppression for longer than 2 years
- CD4 count consistently >300 cells/mm<sup>3</sup>

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV finds value in continuing viral load testing every 3 to 4 months to provide enhanced monitoring of adherence or disease progression among children and youth. Some experts monitor CD4 cell count less frequently (e.g., every 6 to 12 months) in children and adolescents who are adherent to therapy and have CD4 cell count values well above the threshold for OI risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years.<sup>10</sup> Some clinicians find value in visits every 3 months even when lab testing is not performed, in order to review adherence and update dosing for interim growth.

## ***Testing at the Time of Switching Antiretroviral Therapy***

When a switch in regimen is made to simplify ART, labs appropriate to the toxicity profile of the new regimen should be measured at baseline. Follow-up should include plasma viral load at 4 weeks (and not more than 8 weeks) after the switch to ensure efficacy of the new regimen. If the regimen is switched because of ART failure (see [Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy](#)), resistance testing should be performed while a patient is still receiving the failing regimen. This optimizes the chance of identifying resistance mutations because resistant strains may revert to wild type within a few weeks of stopping ARV drugs (see [Antiretroviral Drug-](#)

[Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). Among children with prolonged or repeated periods of viral nonsuppression in the face of serial ART regimens, phenotypic resistance testing, including co-receptor tropism testing, should be considered in addition to genotypic viral resistance testing.<sup>11</sup>

## Immunologic Monitoring in Children: General Considerations

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

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

While guidelines now recommend that children of all ages and adults receive ART regardless of CD4 count and clinical stage, CD4 count-associated risk profiles contribute to the level of urgency for recommendations on when to initiate therapy in a treatment-naïve child with HIV infection **and when to assess need for OI prophylaxis** (see [When to Initiate](#)). A meta-analysis from the HPPM Collaborative Study generated plots which can be used to estimate the short-term risk of progression to AIDS or death in the absence of effective ART according to age and the most recent CD4 percentage/absolute CD4 cell count or HIV-1 RNA viral load measurement.<sup>14</sup>

Measurement of CD4 cell count and percentage can be associated with considerable inpatient variation.<sup>15</sup> Mild intercurrent illness, the receipt of vaccinations, or exercise can produce a transient decrease in CD4 cell count and percentage; thus, CD4 cell count and percentage are best measured when patients are clinically stable. **Clinical decisions, especially those concerning therapy changes, should be made in response to confirmed changes in CD4 cell count/percentage in conjunction with a confirmed viral load determination,** with a minimum of 1 week between measurements.

## HIV RNA Monitoring in Children: General Considerations

Quantitative HIV-1 RNA assays measure the plasma concentration of HIV RNA as copies/mL, commonly referred to as the plasma viral load. Without therapy, plasma viral load initially rises to high peak levels during the period of primary infection in adults and adolescents, and then it declines by as much as 2 to 3 log<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 living with HIV, the stable lower level (or viral 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 load persists 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 over 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 an immature but 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 data indicating that high plasma viral load is associated with disease progression, the predictive value of specific HIV RNA concentrations for disease progression and death for an individual child is moderate.<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 in older children.<sup>20</sup> In both children and adults living with HIV, CD4 cell count or percentage and plasma viral load are independent predictors of disease progression and mortality risk, and use of the two markers together more accurately defines prognosis.<sup>23,24,26,27</sup>

### ***Methodological Considerations in Interpretation and Comparability of HIV RNA Assays***

Based on accumulated experience with currently available assays, viral suppression is currently defined as a plasma viral load below the detection limit of the assay used (generally <20 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](#)).<sup>28</sup> Temporary viral load elevations (“blips”) between the level of detection and 500 copies/mL often are detected in adults<sup>29</sup> and children on ART and should not be considered to represent virologic failure as long as the values return to below the level of detection at the time of repeat testing. For definitions and management of virologic treatment failure, see [Recognizing and Managing Antiretroviral Treatment Failure](#) in [Management of Children Receiving Antiretroviral Therapy](#). These definitions of viral 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 two-fold (0.3 log<sub>10</sub> copies/mL) or more.<sup>30,31</sup> Because of the variability among assays in techniques and quantitative HIV RNA measurements, a single HIV RNA assay method should be used consistently to monitor an individual patient when possible.<sup>32-34</sup>

The predominant HIV-1 subtype in the United States is subtype B—the subtype for which all initial assays were targeted. Current kit configurations for all companies have been designed to detect and quantitate essentially all viral subtypes (see [Diagnosis of HIV Infection](#)). 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>32,35-39</sup> It is particularly relevant for children who are born outside the United States or to foreign-born parents.

Biologic variation in plasma viral load within one person is well documented. In adults, repeated measurement of plasma viral load using the same assay can vary by as much as three-fold (0.5 log<sub>10</sub> copies/mL) in either direction over the course of a day or on different days.<sup>26,31</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, on repeated testing, only differences greater than five-fold (0.7 log<sub>10</sub> copies/mL) in infants younger than 2 years and greater than three-fold (0.5 log<sub>10</sub> copies/mL) in children aged 2 years and older 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. Interpretation of plasma viral load for clinical decision making should be done by or in consultation with an expert in pediatric HIV infection because of the complexities of HIV RNA testing and the age-related changes in plasma viral load in children.

### ***Genetic Testing for Management of HIV***

The evaluation of human and pathogen genes is increasingly being employed to manage disease intervention, and this approach to treatment is featured in the rise of precision medicine. Clinicians who manage HIV have routinely probed HIV’s genetic sequences for mutations 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>40,41</sup> In addition, some human genetic polymorphisms are associated with drug toxicity or adverse events (e.g., using HLA-B\*5701 testing to predict abacavir hypersensitivity). Future clinical practice is likely to feature broader applications of multiple forms of genetic testing to guide management of health and disease.

**Table 3. Sample Schedule for Clinical and Laboratory Monitoring of Children Before and After Initiation of Antiretroviral Therapy**

	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>	Only Required Every 6–12 Months <sup>e</sup>	ARV Switch
History and Physical	√	√	√	√	√	√		√
Adherence Evaluation		√	√	√	√	√		√
CD4 Count	√	√	√			√		√
Plasma Viral Load	√	√	√		√	√		√
Resistance Testing	√							√
CBC with Differential	√	√	√		√	√		√
Chemistries <sup>f</sup>	√	√	√		√	√		√
Lipid Panel	√		√				√	
Random Plasma Glucose <sup>g</sup>			√				√	
Urinalysis	√		√				√	
Hepatitis B Screening <sup>h,i</sup>		√						√

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

<sup>b</sup> Readiness for ARV adherence is assessed prior to starting ART. If abacavir is being considered as part of the regimen, send HLA-B\*5701 testing prior to initiation of that ARV and choose an alternative ARV if HLA-B\*5701 is positive (see [Abacavir](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)). Genotype resistance testing is recommended if not already performed (see [Antiretroviral Drug-Resistance Testing](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). Send tests appropriate to the toxicities expected from each patient's ART regimen and history (see text).

<sup>c</sup> If ART is initiated within 30 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 and have CD4 cell values well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years. **Viral load testing every 3 to 4 months is generally recommended to monitor ARV adherence.**

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

**Chemistries refer to a comprehensive metabolic panel.**

**Random plasma glucose collected in a gray top tube.**

<sup>h</sup> Recommended when considering starting ARV drugs with activity against hepatitis B, specifically lamivudine-, emtricitabine-, and tenofovir-containing regimens.

<sup>i</sup> Recommended only when individual previously demonstrated no immunity to hepatitis B.

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; CBC = complete blood count; CD4 = CD4 T lymphocyte; TDF = tenofovir disoproxil fumarate

**Table 4. Primary, FDA-Approved Assays to Monitor Viral Load**

Assay	Abbott Real Time	NucliSens EasyQ v 2.0	COBAS Ampliprep/TaqMan v 2.0	Versant v 1.0
Method	Real-time RT-PCR	Real-time NASBA	Real-time RT-PCR	Real-time RT-PCR
Dynamic Range (copies/mL)	40–10 <sup>7</sup>	25–10 <sup>7</sup>	20–10 <sup>7</sup>	37–11x10 <sup>7</sup>
Specimen volume <sup>a</sup>	0.2–1 mL	0.1–1 mL	1 mL	0.5 mL
Manufacturer	Abbott	bioMerieux	Roche	Siemens

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

**Key to Acronyms:** FDA = Food and Drug Administration; NASBA = nucleic acid sequence-based amplification; RT-PCR = reverse transcription polymerase chain reaction

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## General Considerations

Since the introduction of potent combination antiretroviral (ARV) drug regimens in the mid-1990s, the treatment of pediatric HIV has steadily improved. These potent regimens have the ability to suppress viral replication, thus lowering the risk of virologic failure due to the development of drug resistance. Antiretroviral therapy (ART) that includes at least three drugs from at least two drug classes are recommended; such regimens have been associated with enhanced survival, reduction in opportunistic infections and other complications of HIV infection, improved growth and neurocognitive function, and improved quality of life in children.<sup>1-4</sup> In the United States and the United Kingdom, significant declines in morbidity, mortality, and hospitalizations have been reported in children living with HIV between 1994 and 2006, concomitant with increased use of highly active combination regimens.<sup>5-7</sup> As a result, children with perinatal HIV infection are now living into the third and fourth decades of life, and potentially beyond.

The increased survival of children with HIV is associated with challenges in selecting successive new ARV drug regimens. In addition, therapy is associated with short- and long-term toxicities, which can be recognized in childhood or adolescence (see [Management of Medication Toxicity or Intolerance](#)).<sup>8-12</sup>

ARV drug-resistant virus can develop during ART when viral replication occurs in the presence of subtherapeutic ARV concentrations caused by poor adherence, poor absorption, a regimen that is not potent, or a combination of these factors. In addition, primary drug resistance may be seen in ARV-naïve children who have contracted a resistant virus.<sup>13-17</sup> Thus, decisions about which drugs to choose for ARV-naïve children (see [What to Start](#)) and how to best treat ARV-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV should be directed by or made in consultation with a specialist in pediatric HIV infection. Treatment of ARV-naïve children (including information on when to start treatment and which drugs to use), when to change therapy, and treatment of ARV-experienced children are discussed in separate sections of the guidelines. For guidance about treatment of **sexually mature adolescents**, see the [Adult and Adolescent Guidelines](#).

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

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

- **Age (treatment initiation is urgent for infants aged <12 months)**
- Severity of HIV disease and risk of disease progression, as determined by presence (see [When to Initiate](#)) or history of HIV-related illnesses, and degree of CD4 immunosuppression, (see [Revised Surveillance Case Definition for HIV Infection](#))

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

- Availability of appropriate (and palatable) drug formulations and pharmacokinetic (PK) information on appropriate dosing in a child's age/weight group;
- Potency, complexity (e.g., dosing frequency, food requirements), and potential short- and long-term adverse effects of the ART regimen;

- Effect of initial regimen choice on later therapeutic options;
- A child's ART history;
- Presence of ARV drug-resistant virus;
- Presence of comorbidity, such as tuberculosis, hepatitis B or C virus infection, or chronic renal or liver disease, that could affect decisions about drug choice and the timing of therapy initiation;
- Potential ARV drug interactions with other prescribed, over-the-counter, or complementary/alternative medications taken by a child; and
- The anticipated ability of the caregiver and child to adhere to the regimen.

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

## Goals of Antiretroviral Treatment

Currently available ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV, due to persistence of HIV in CD4 lymphocytes and other **long-lived** cells.<sup>20-22</sup> This was demonstrated when a child with HIV who was treated with ART at 30 hours of age experienced viremic rebound after more than 2 years of undetectable HIV RNA levels while off ART.<sup>23,24</sup> There are data to suggest that, after viral suppression, the mean half-life of intracellular HIV proviral DNA **can be up to almost 16 years.**<sup>25</sup> Thus, based on currently available data, HIV causes a chronic infection that likely requires life-long treatment once a child starts therapy. The goals of ART for children living with HIV include:

- Preventing and reducing HIV-related morbidity and mortality;
- Restoring and/or preserving immune function as reflected by CD4-cell measures;
- Maximally and durably suppressing viral replication;
- Preventing emergence of viral drug-resistance mutations;
- Minimizing drug-related toxicity;
- Maintaining normal physical growth and neurocognitive development;
- Improving quality of life; and
- **Preventing transmission of HIV to others**

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

## *Use and Selection of Combination Antiretroviral Therapy*

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

## ***Drug Sequencing and Preservation of Future Treatment Options***

The choice of ARV treatment regimens should include consideration of future treatment options, such as the presence of or potential for drug resistance. Multiple changes in ARV drug regimens can rapidly exhaust treatment options and should be avoided. Appropriate sequencing of drugs for use in initial and second-line therapy can preserve future treatment options and is another strategy to maximize long-term benefit from therapy. Current recommendations for initial therapy are to use two classes of drugs (see [What to Start](#)), thereby sparing three classes of drugs for later use.

## ***Maximizing Adherence***

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

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# When to Initiate Therapy in Antiretroviral-Naive Children (Last updated May 22, 2018; last reviewed May 22, 2018)

## Overview

The Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends initiation of therapy for all adults and adolescents with HIV (see the [Adult and Adolescent Guidelines](#)). In addition to trials demonstrating the benefits of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,<sup>1</sup> a randomized clinical trial has shown definitive benefit to initiating ART in asymptomatic adults with CD4 cell counts >500 cells/mm<sup>3</sup>. The START trial randomized 4,685 antiretroviral (ARV)-naive adults with HIV (median age: 36 years) with CD4 cell counts >500 cells/mm<sup>3</sup> to immediately initiate ART or defer ART until their CD4 cell counts declined to <350 cells/mm<sup>3</sup> or until the development of any condition that dictated use of ART. There were 42 primary endpoints (AIDS, serious non-AIDS events, or death) among those enrolled in the study's early treatment group, compared with 96 in the deferred treatment group, for an overall 57% reduction in risk of serious illness or death with early treatment ( $P < 0.001$ ). It should be noted that the absolute risk for the primary endpoint was low: 3.7% in the deferred arm versus 1.8% in the immediate treatment arm. Sixty-eight percent of the primary endpoints occurred in patients with CD4 cell counts >500 cells/mm<sup>3</sup>. The risks of Grade 4 events or unscheduled hospital admissions were similar in the two groups.<sup>2</sup>

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

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) also recommends treatment for all children with HIV. However, the urgency for immediate initiation varies by age and pretreatment CD4 cell count, due to fewer available data regarding benefits and risks of immediate therapy in asymptomatic children with HIV than in adults. Concerns about adherence and toxicities become particularly important when therapy in children is initiated at an early age and will likely be life-long. In children aged <1 year, the benefit of immediate ART has been clearly demonstrated in the CHER trial.<sup>6</sup> In addition, Shiao et al. reported that among two cohorts of infants with HIV in Johannesburg, South Africa, infants who initiated ART aged <6 months had better sustained viral control after achieving suppression than infants starting therapy between the ages of 6 and 24 months.<sup>7</sup> Data in older children are equivocal. The PREDICT trial, which enrolled children 1 to 12 years of age (median age: 6.4 years), found that the risk of clinical progression was extremely low in both children receiving immediate ART and delayed (CD4-based) ART; additionally, no clinical benefit of immediate ART was observed.<sup>8</sup> In contrast, in an observational study including over 20,000 children ages 1 to 16 years from 19 cohorts in Europe, Southern Africa, and West Africa, immediate ART was associated with lower mortality and better growth in children aged <10 years when compared with ART that was delayed until CD4 count decreased to <350 cells/mm<sup>3</sup>. In children aged >10 years at enrollment, there was no difference in mortality or growth associated with immediate ART initiation.<sup>9</sup>

Immediate therapy in the early stages of HIV infection in both children and adults could potentially control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species. Initiation of therapy at higher CD4 cell counts has been associated with fewer drug resistance mutations at virologic failure in adults.<sup>10</sup> Early therapy also preserves immune function, preventing clinical disease progression.<sup>11,12</sup> Ongoing viral replication may be associated with persistent inflammation and development of cardiovascular,

kidney, and liver disease and malignancy; studies in adults also suggest that early control of replication may reduce the occurrence of these non-AIDS complications.<sup>11,13-15</sup> Conversely, delaying therapy until later in the course of HIV infection may result in reduced evolution of drug-resistant virus due to a lack of drug selection pressure, improved adherence to the therapeutic regimen due to perceived need when the patient becomes symptomatic, and reduced or delayed adverse effects of ART.

## Treatment Recommendations for Initiation of Therapy in Antiretroviral-Naive Infants and Children with HIV

Panel's Recommendations		
Aged	Criteria	Recommendation
<12 Months <sup>a</sup>	Regardless of clinical symptoms, immune status, or viral load	Urgent <sup>b</sup> treatment ( <b>All</b> except <b>AI</b> for children aged ≥6 weeks to <12 weeks)
1 to <6 Years	CDC Stage 3-defining opportunistic illnesses <sup>c</sup>	Urgent <sup>b</sup> treatment ( <b>AI*</b> )
	CDC Stage 3 immunodeficiency: <sup>d</sup> CD4 <500 cells/mm <sup>3</sup>	
	Moderate HIV-related symptoms <sup>c</sup>	Treat <sup>e</sup> ( <b>All</b> )
	CD4 cell count <sup>c</sup> 500–999 cells/mm <sup>3</sup>	
	Asymptomatic or mild symptoms <sup>c</sup> <b>and</b> CD4 cell count <sup>c</sup> ≥1000 cells/mm <sup>3</sup>	Treat <sup>e</sup> ( <b>AI*</b> )
≥6 Years <sup>e</sup>	CDC Stage 3-defining opportunistic illnesses <sup>c</sup>	Urgent <sup>a</sup> treatment ( <b>AI*</b> )
	CDC Stage 3 immunodeficiency: <sup>d</sup> CD4 <200 cells/mm <sup>3</sup>	
	Moderate HIV-related symptoms <sup>c</sup>	Treat <sup>b</sup> ( <b>All</b> )
	CD4 cell count <sup>d</sup> 200–499 cells/mm <sup>3</sup>	
	Asymptomatic or mild symptoms <sup>c</sup> <b>and</b> CD4 cell count ≥500 cells/mm <sup>3</sup>	Treat <sup>e,f</sup> ( <b>AI*</b> )
<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 and adolescents but not studies limited to post-pubertal adolescents</p>		

**Note:** Adherence should be assessed and discussed with children who have HIV and their caregivers before initiation of therapy (**All**).

<sup>a</sup> Treatment of infants aged ≤2 weeks is complex and an area of active investigation. See Antiretroviral Management of Newborns with Perinatal HIV

<sup>b</sup> Within 1–2 weeks, including an expedited discussion on adherence.

<sup>c</sup> See [Table 6](#) for definitions.

<sup>d</sup> CD4 cell counts should be confirmed with a second test to meet the treatment criteria before initiation of ART.

<sup>e</sup> More time can be taken to fully assess and address issues associated with adherence with the caregivers and the child prior to initiating therapy. Patients/caregivers may choose to postpone therapy, and on a case-by-case basis, providers may elect to defer therapy based on clinical and/or psychosocial factors, with close patient monitoring.

<sup>f</sup> For initiation of ART for adolescents aged ≥13 years and SMR of 4 or 5, see the [Adult and Adolescent Guidelines](#).

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

## Infants Younger Than 12 Months

The CHER trial, a randomized clinical trial in South Africa, demonstrated that initiating triple-drug ART at ages 6 to 12 weeks in asymptomatic infants with perinatally acquired HIV who had normal CD4 percentages (>25%) resulted in a 75% reduction in early mortality, compared with delaying treatment until the infants met clinical or immune criteria.<sup>6</sup> Most of the deaths of the infants in the delayed treatment arm occurred in the first 6 months after study entry. A substudy of this trial also found that infants treated early had significantly better gross motor and neurodevelopmental profiles than those in whom therapy was deferred.<sup>16</sup> Additionally, infants treated early had decreased immune activation, greater recovery of CD4 cells, expanded CD4-naïve T cells, and retention of innate effector frequencies, resulting in greater immune reconstitution than that achieved with deferred ART.<sup>17</sup> **Shiau et al. reported that, among two cohorts of South African infants with HIV, those who initiated ART aged <6 months had better sustained viral control after achieving suppression than did infants starting therapy between 6 and 24 months.**<sup>7</sup> A 2011 surveillance study followed infants with recently diagnosed HIV who were aged <24 months (n = 272, median age: 6.1 months) from five inpatient or outpatient settings in Johannesburg, South Africa. By 6 months post-enrollment, 53 infants (19.5%) had died and 73 infants (27%) were lost to follow-up. Despite these discouraging results, there was a 71% reduction in the 6-month risk of death among the children who initiated ART, and infants identified through routine prevention of perinatal transmission or immunization clinics were five times less likely to die than those diagnosed with HIV during a symptomatic hospital admission.<sup>7,18</sup> Because the risk of rapid progression is so high in young infants, and based on the data in young infants from the CHER study, the Panel recommends urgent initiation of therapy (within 1–2 weeks) for all infants aged <12 months regardless of clinical status, CD4 percentage, or viral load (see [Box Recommendations](#)). Before therapy is initiated, it is important to assess, discuss, and address issues associated with adherence with an infant’s caregivers. However, given the high risk of disease progression and mortality in young infants with HIV, it is important to expedite this assessment in infants aged <12 months, and provide increased, intensive follow-up in the first few weeks to support the caregiver. The risk of disease progression is inversely correlated with the age of a child, with the youngest infants at greatest risk of rapid disease progression. Progression to moderate or severe immune suppression is also frequent in older, **untreated** infants with HIV; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.<sup>19</sup> In the HPPMC study meta-analysis, the 1-year risk of AIDS or death was substantially higher in younger children than in older children at any given level of CD4 percentage, particularly for infants younger than 12 months.<sup>20</sup> Although the risk of progression is greatest during the first year of life, clinical and laboratory parameters are limited in their ability to determine which young infants are at risk of rapid disease progression. No specific “at-risk” viral or immunologic threshold can be easily identified, and progression of HIV disease and opportunistic infections (OIs) can occur in young infants with normal CD4 cell counts.<sup>20</sup>

Identification of HIV infection during the first few months of life permits clinicians to initiate ART during the initial phases of primary infection. Consistent with the CHER trial, data from a number of observational studies in the United States and Europe demonstrate that infants who receive early treatment are less likely to progress to AIDS or death and have improved growth compared to those who start therapy later.<sup>11,21–23</sup> Several small studies have demonstrated that, despite the very high levels of viral replication in infants with perinatally acquired HIV, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.<sup>24,25</sup> In infants with sustained control of plasma viremia, failure to detect extra-chromosomal replication intermediates suggests near-complete control of viral replication can be achieved.<sup>26,27</sup> Early initiation of suppressive ART (i.e., aged <6 months) results in a significant proportion of infants with HIV who clear maternally-acquired antibodies to HIV but fail to produce their own HIV-specific antibody, thus testing **reveals them to be** HIV-seronegative; however, viral reservoirs remain, as demonstrated by viral rebound if ART is stopped.<sup>26,28–31</sup> Although there is a single case report of a **27-month** remission in a child with HIV infection (discussed below), current ART has not been shown to eradicate HIV infection in infants with perinatally acquired HIV because of persistence of HIV in CD4 and other long-lived cells.<sup>32–34</sup> **For these reasons, the Panel does not recommend empiric treatment interruption.**



The report of a prolonged remission in a child with perinatally acquired HIV in Mississippi generated discussion about early initiation of ART in newborn infants with high-risk HIV exposure. This newborn, born to a mother who did not receive antenatal or perinatal ART, was treated with a three-drug ART regimen at age 30 hours through age 18 months, after which ART was 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 was confirmed with repeat testing.** ART was restarted at that time.<sup>35,36</sup> This experience has prompted increasing support for initiation of treatment in the first weeks of life, as soon as the diagnosis is made. However, **managing neonates with HIV is complex from both a medical and social perspective.** Because of limited safety and pharmacokinetic data and experience with ARV drugs in infants aged <2 to 4 weeks, particularly among premature infants, drug and dose selection in this age group is challenging (see [What to Start](#) and [Antiretroviral Management of Newborns](#)).<sup>37</sup> **In a single-center, retrospective review of 22 infants with HIV who started ART in the first month of life (median: 13.5 days) in Cape Town, South Africa, only half remained in care at a mean age of 2.1 years, and only two had viral suppression <50 copies/mL when last measured.**<sup>38</sup>

Virologic suppression may take longer to achieve in young children than in older children or adults.<sup>39-41</sup> Possible reasons for the slower response in infants include higher virologic set points in young infants, inadequate ARV drug concentrations, and poor adherence because of the difficulties in administering complex regimens to infants. With currently available drug regimens, rates of viral suppression of 70% to 80% have been reported in infants with HIV initiating therapy aged <12 months.<sup>11,42,43</sup> In a 5-year follow-up study of 40 children with HIV who initiated treatment aged <6 months, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.<sup>11</sup>

More rapid viral suppression in young infants may be important in reducing the long-lived HIV reservoirs. Several studies comparing children initiating ART before age 12 weeks to those initiating ART at age 12 weeks to 1 to 2 years have found that the size of the viral reservoir (as measured by peripheral blood mononuclear cell [PBMC] HIV-1 DNA levels) after 1 and 4 years of ART significantly correlated with age at ART initiation and age at viral control.<sup>44-46</sup> Similarly, in a cross-sectional study of 144 youth with perinatally acquired HIV with long-term viral suppression, PHACS/AMP found a lower proviral reservoir in those who achieved virologic control at <1 year versus 1 to 5 years versus >5 years of age (4.2 vs. 19.4 vs. 70.7 copies/million PBMCs, respectively).<sup>47</sup> **In addition, among 61 children with perinatally acquired HIV in PHACS/AMP who achieved viral suppression aged <1 year versus aged between 1 and 5 years, the mean half-life of HIV DNA from viral suppression was shorter in the early suppressors—5.9 years versus 18.8 years, respectively.**<sup>48</sup>

Information on appropriate drug dosing in infants aged <3 months, and particularly preterm infants, is limited.<sup>37</sup> Hepatic and renal functions are immature in newborns, who are undergoing rapid maturational changes during the first few months of life. This can result in substantial differences in ARV dose requirements between young infants and older children.<sup>49</sup> When drug concentrations are sub-therapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence, ARV drug resistance can develop rapidly, particularly in the setting of high levels of viral replication in young infants. Frequent follow-up for dose optimization during periods of rapid growth and continued assessment and support of adherence are especially important when treating young infants (see [Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV](#)).

Finally, the possibility of long-term toxicities (e.g., lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, mitochondrial dysfunction) with prolonged therapy is a concern.<sup>50</sup> However, the clear benefit of immediate ART in reducing mortality and morbidity in infants outweighs such potential risks.

## Children Aged 1 Year and Older

In general, disease progression is less rapid in children aged  $\geq 1$  year.<sup>19</sup> However, children with Centers for Disease Control and Prevention (CDC) Clinical Stage 3-defining OIs (see [Revised Surveillance Case Definition for HIV Infection](#) and [Table 6](#)) are at high risk of disease progression and death. The Panel recommends urgent treatment (i.e., within 1–2 weeks) for all such children with severe HIV disease, regardless of immunologic or virologic status. In these cases, the clinical team should expedite a discussion on adherence and provide increased, intensive follow-up in the first few weeks to support the children and families. Children aged  $\geq 1$  year who have mild to moderate clinical symptoms (see [Table 6](#)) or who are asymptomatic are at lower risk of disease progression than children with more severe clinical symptoms.<sup>51</sup> ART is also recommended for these children, but because of the lower risk of rapid disease progression, more time can be taken to fully assess, discuss and address issues associated with adherence with the caregivers and the children prior to initiating therapy.

The Cochrane Collaboration<sup>52</sup> published a review on the effectiveness of ART in children with HIV aged  $< 2$  years based on data from published randomized trials of early versus deferred ART.<sup>6,53</sup> The authors concluded that immediate therapy reduces morbidity and mortality and may improve neurologic outcome, but that data were less compelling in support of universal initiation of treatment between ages 1 and 2 years.

The PREDICT multicenter, open-label trial randomized 300 children with HIV **aged 1 to 12 years at enrollment** (median: 6.4 years) to immediate initiation of ART or deferral until the CD4 percentage was  $< 15\%$ .<sup>54</sup> AIDS-free survival at 144 weeks was 98.7% (95% CI, 94.7–99.7) in the deferred group and 97.9% (95% CI, 93.7–99.3) in the immediate therapy group ( $P = 0.6$ ), and immediate ART did not significantly improve neurodevelopmental outcomes.<sup>8</sup> However, because of the low event rate, the study was underpowered to detect a difference between the two groups. The trial did show better height gain for children who started ART immediately.<sup>54</sup> This study population likely had a selection bias toward relatively slowly progressive disease because it enrolled children who had survived a median of 6 years without ART. The low enrollment of children aged  $< 3$  years limits its value in making recommendations in that age group.

**A retrospective analysis of 245 Brazilian children with perinatally acquired HIV who initiated ART between 2002 and 2014 at a median of 52 months of age (IQR 18–94) found there was no statistical difference in mortality among children who initiated ART at  $< 18$  months of age (7.9%) compared with those who initiated ART after development of symptoms or aged  $> 18$  months (12.4%). However, because the median age of the late presenters was approximately 5 years, the results do not take into consideration children with rapidly progressive disease who may have died prior to HIV diagnosis and those who presented later may have been slow progressors with a better prognosis.**<sup>55</sup>

In contrast, a general trend toward lower mortality and better growth with earlier ART initiation was reported in an evaluation of observational data from 20,756 ART-naïve children aged 1 to 16 years at enrollment from 19 cohorts in Europe, Southern Africa, and West Africa.<sup>9</sup> After 5 years of follow-up, there was lower mortality and higher mean height-for-age z-score with immediate ART initiation versus delaying until CD4 count decreased to  $< 350$  cells/mm<sup>3</sup> in children aged  $< 10$  years at enrollment. The best outcomes were observed in European children, who attained growth outcomes comparable to children without HIV. However, in those aged  $> 10$  years at enrollment, neither benefit nor harm was observed with immediate ART.

As with data in adults, data from pediatric studies suggest that improvement in immunologic parameters is better in children when treatment is initiated at higher CD4 percentage/count levels.<sup>56–60</sup> In the PENPACT-1 clinical trial,  $> 90\%$  of children recovered a normal CD4 cell count when ART was initiated during “mild” immunosuppression at any age, or with “advanced” immunosuppression at  $< 3$  years of age. Observational studies in children have reported similar findings. Among 1,236 children with perinatally acquired HIV in the United States, only 36% of those who started treatment with CD4 percentage  $< 15\%$  achieved CD4 percentage  $> 25\%$  after 5 years of therapy, compared with 59% of children starting with CD4 percentages of 15% to 24%.<sup>61</sup> Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.<sup>23,24,61,62</sup>

Additionally, delaying ART initiation to older childhood was found to substantially delay pubertal development and menarche, independent of immune suppression, in Ugandan and Zimbabwean children with HIV in the ARROW trial.<sup>63</sup> Finally, the PREDICT study demonstrated improved height *z*-scores in the early treatment arm compared with no improvement in the deferred arm.<sup>54</sup> These combined data suggest that initiation of ART at higher CD4 values and younger ages maximizes the potential benefit for immunologic recovery and normalization of growth.

There are potential concerns regarding starting life-long ART in all children. Drug choices are more limited in children than in adults and adequate data to address the potential long-term toxicities of prolonged ART in a developing child are not yet available. Some studies have shown that a small proportion of children with perinatally acquired HIV may be long-term non-progressors, with no immunologic or clinical progression by age 10 years despite receiving no ART.<sup>64-66</sup> Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in childhood is often challenging.<sup>67</sup> Incomplete adherence leads to the selection of viral resistance mutations, but forced administration of ARV drugs to children may result in treatment aversion or fatigue, which occurs among many children with perinatally acquired HIV during adolescence.<sup>68</sup>

Despite this, a number of studies have found evidence for the long-term benefits of early ART, including reduced mortality in children aged <10 years,<sup>9</sup> improved growth and pubertal outcomes, improved immune reconstitution, and reduced inflammation in children and adolescents. The Panel believes the benefits of early ART initiation outweigh potential risks, and recommends initiation of ART for all children regardless of clinical, immunologic, or virologic status.

Similar recommendations have been made by European pediatric HIV experts in the 2016 Pediatric European Network for Treatment of AIDS Treatment Guidelines.<sup>69</sup> The Panel has formulated recommendations related to the urgency of ART initiation based on age, clinical status, and CD4 cell count (see [Box Recommendations](#)). **The Panel has also rated the available evidence. In general, ART should be started urgently (i.e., within 1–2 weeks of HIV diagnosis) in infants aged <12 months and in children with advanced HIV infection. For other children initiating therapy, ART may be delayed long enough to educate** caregivers (and children, as appropriate) about regimen adherence and to anticipate and resolve any barriers that might diminish adherence. This is particularly true for children aged ≥5 years, given their lower risk of disease progression.

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

- Increasing HIV RNA levels;
- Declining CD4 cell count or percentage values (e.g., approaching CDC Stage 3);
- Development of new clinical symptoms; and
- The ability of caregiver and child to adhere to the prescribed regimen.

**Table 5. HIV Infection Stage<sup>a</sup> Based on Age-Specific CD4 Cell Count or Percentage**

Stage	Age on Date of CD4 Test					
	<1 Year	%	1 to <6 Years	%	≥6 Years	%
	Cells/μL		Cells/μL		Cells/μL	
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

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

Source: Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR* 2014;63(No. RR-3):1-10.

**Key to Acronyms:** CD4 = CD4 T lymphocyte

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

Mild HIV-Related Symptoms
<p>Children with 2 or more of the conditions listed, but none of the conditions listed in Moderate Symptoms category:</p> <ul style="list-style-type: none"> <li>• Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 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>
Moderate HIV-Related Symptoms
<ul style="list-style-type: none"> <li>• Anemia (hemoglobin &lt;8 g/dL [<math>&lt;80</math> g/L]), neutropenia (white blood cell count &lt;1,000/μL [<math>&lt;1.0 \times 10^9</math>/L]), and/or thrombocytopenia (platelet count &lt;100 × 10<sup>3</sup>/μL [<math>&lt;100 \times 10^9</math>/L]) persisting for ≥30 days</li> <li>• Bacterial meningitis, pneumonia, or sepsis (single episode)</li> <li>• Candidiasis, oropharyngeal (thrush), persisting (&gt;2 months) in children aged &gt;6 months</li> <li>• Cardiomyopathy</li> <li>• Cytomegalovirus infection, with onset before 1 month</li> <li>• Diarrhea, recurrent or chronic</li> <li>• Hepatitis</li> <li>• Herpes simplex virus (HSV) stomatitis, recurrent (&gt;2 episodes within 1 year)</li> <li>• HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month</li> <li>• Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 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 &gt;1 month)</li> <li>• Toxoplasmosis, onset before 1 month</li> <li>• Varicella, disseminated (complicated chickenpox)</li> </ul>

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

Stage-3-Defining Opportunistic Illnesses in HIV Infection
<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<sup>b</sup></li><li>• Coccidioidomycosis, disseminated or extrapulmonary</li><li>• Cryptococcosis, extrapulmonary</li><li>• Cryptosporidiosis, chronic intestinal (&gt;1 month duration)</li><li>• Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age &gt;1 month</li><li>• Cytomegalovirus retinitis (with loss of vision)</li><li>• Encephalopathy attributed to HIV<sup>c</sup></li><li>• HSV: chronic ulcers (&gt;1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age &gt;1 month)</li><li>• Histoplasmosis, disseminated or extrapulmonary</li><li>• Isosporiasis, chronic intestinal (&gt;1 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><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>b</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>c</sup></li></ul>

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

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

<sup>c</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).

Modified from:

- Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).
- Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. *MMWR*. 2014;63(No. RR-3):1-10.

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# What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated May 22, 2018; last reviewed May 22, 2018)

## Panel's Recommendations

- The selection of an initial regimen should be individualized based on several factors, including characteristics of the proposed regimen, patient characteristics, drug efficacy, potential adverse effects, patient and family preferences, and 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, including either an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a boosted protease inhibitor, plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone (AI\*).
- Table 7 provides a list of Panel-recommended regimens that are designated as Preferred or Alternative; recommendations vary by 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 provide direct comparisons of 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 adult studies, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 T lymphocyte (CD4) cell count and HIV RNA levels. The Panel continually modifies recommendations on optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities are recognized.

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

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., syrups vs. powders), volume of syrups, and pill size/number of pills;
- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

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

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

## Factors to Consider When Selecting an Initial Regimen

An ART regimen for children should generally consist of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus one active drug from the following classes: integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI). Choice of a regimen should be individualized based on several factors, including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Drug recommendations often include both age and weight limitations. Although age can be used as a rough guide, body weight—when available—is the preferred determinant of the recommendation for selecting a specific drug (except for infants aged <14 days). When FDA approvals are based solely on weight, the Panel has suggested an approximate age for administration. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in [Table 8](#). Additional information regarding advantages and disadvantages of drug combinations can be found in the [Adult and Adolescent Guidelines](#). Specific information about clinical efficacy, adverse events (AEs), and dosing recommendations for each drug can be found in [Appendix A: Pediatric Antiretroviral Drug Information](#). In addition, because ART will most likely need to be administered throughout the patient's life, clinicians should consider potential barriers to adherence, including the complexity of schedules and food requirements for different regimens, differing formulations, palatability problems, and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after assessment and counseling of caregivers about adherence to therapy.

Emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) have antiviral activity and efficacy against hepatitis B and should be considered for use in children with coinfection. For a comprehensive [review of this topic](#), as well as [hepatitis C](#) and [tuberculosis](#) during HIV coinfection, see the [Pediatric Opportunistic Infections Guidelines](#).

## Choosing Between an Integrase Strand Transfer Inhibitor-, a Non-Nucleoside Reverse Transcriptase Inhibitor-, or a Boosted Protease Inhibitor-Based Initial Regimen

*Preferred* regimens for initial therapy include INSTI-, NNRTI-, or boosted PI-based regimens. The choice of regimen should be based on patient characteristics, especially age, the results of viral drug resistance testing, drug efficacy and AEs, patient and family preference, pill size, and dosing frequency. **Because adherence to the prescribed regimen is necessary, assessing patient and family preference should be weighed with this in mind.**

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 superiority of a lopinavir/ritonavir (LPV/r)-based regimen compared to a nevirapine (NVP)-based regimen in infants and children aged 2 months to 35 months, regardless of prior 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 and 40.1% of children, respectively.<sup>1</sup>

- Those in the NVP group demonstrated greater, but not statistically significant, improvements in **CD4 counts** and the participants' growth parameters. **However, improvements in CD4 cell counts were only maintained up to 1 year after initiation of ART.**<sup>2</sup> Similar improved immune and growth parameters were also demonstrated in the NEVEREST study, where these parameters were compared in children who switched to a NVP regimen and those who continued on a LPV/r regimen after achieving virologic control.<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 specific NNRTI or PI initiated). In the PI-based group, 49% of children received LPV/r and 48% received nelfinavir; in the NNRTI-based group, 61% of children received EFV and 38% received NVP. After 4 years of follow-up, 73% of children randomized to receive PI-based therapy and 70% randomized to receive NNRTI-based therapy remained on their initial ART 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 randomized to receive either an NNRTI- or LPV/r-based ART.<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 HIV RNA levels <400 copies/mL at 48 weeks was 80% in the LPV/r arm versus 76% in the NNRTI arm, a difference of 4% that was not statistically significant (95% CI, -9% to +17%).

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

Based on the above data, the Panel considers the following as *Preferred* regimens for children when used in combination with two NRTIs:

- Aged <14 days: NVP **or raltegravir (RAL)**
- Aged ≥14 days to <3 years: LPV/r **or RAL**
- Aged ≥3 to <6 years: RAL, boosted atazanavir (ATV), or twice-daily boosted darunavir (DRV)
- Aged ≥6 to <12 years: Dolutegravir (DTG; for children weighing ≥30 kg) or boosted ATV
- Aged ≥12 years or body weight as noted for children who have not reached sexual maturity:
  - Weighing ≥30 kg: DTG
  - Weighing ≥35 kg: Elvitegravir/cobicistat (EVG/COBI; only the EVG/COBI-containing fixed-dose combination EVG/COBI/FTC/TAF is recommended at this time)
  - Weighing ≥40 kg: Boosted ATV or once-daily boosted DRV

*Alternative* regimens are shown in [Table 7](#).

## **Integrase Strand Transfer Inhibitor-Based Regimens**

Three INSTIs—DTG, EVG, and RAL—are licensed for the treatment of ARV-naïve adults with HIV. These agents have quickly become the preferred regimen in adults because of their virologic efficacy, lack of drug-

drug interactions, and favorable toxicity profile. RAL is licensed for treatment of **infants and children from birth**. DTG is approved for use in children weighing  $\geq 30$  kg. EVG has been studied in adolescents in two fixed-dose combination regimens and in combination with two NRTIs and ritonavir (RTV) boosting. (Table 8 lists the advantages and disadvantages of INSTIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.)

### ***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-naïve) adolescents<sup>9,10</sup> and 11 treatment-experienced (but INSTI-naïve) children aged  $\geq 6$  years.<sup>11</sup> The drug has a very favorable safety profile and can be given once daily to treat INSTI-naïve patients. **Studies of this drug are ongoing in children as young as 4 weeks of age.**<sup>12</sup>

#### Recommendation:

- Based on the virologic potency and safety profile observed in adult and pediatric studies,<sup>7,9,13</sup> the Panel recommends DTG in combination with a two-NRTI backbone as a *Preferred* INSTI regimen for children and adolescents weighing  $\geq 30$  kg (AI\*).

### ***Elvitegravir***

EVG is an INSTI available as a tablet, a fixed-dose combination tablet containing EVG/COBI/FTC/TDF, and a fixed-dose combination tablet containing EVG/COBI/FTC/TAF. Both fixed-dose combinations are FDA-approved for use in ART-naïve adults with HIV. EVG/COBI/FTC/TAF is FDA-approved for use in ART-naïve children and adolescents weighing  $\geq 25$  kg. COBI is a specific, potent cytochrome P (CYP) 3A inhibitor that has no activity against HIV and is used as a PK enhancer, which allows for once-daily dosing of EVG.

#### Recommendation:

- Based on the virologic potency and safety profile observed in adult and adolescent studies,<sup>14-18</sup> the Panel recommends EVG only in the fixed-dose combination EVG/COBI/FTC/TAF as a *Preferred* INSTI regimen for children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg who have **creatinine clearances (CrCl)  $\geq 30$  mL/min (AI\*)**.
- **EVG/COBI/FTC/TAF is recommended as an *Alternative* INSTI regimen for children aged  $\geq 6$  years to 12 years and weighing  $\geq 25$  kg who have CrCl  $\geq 30$  mL/min (AI\*).**<sup>19</sup>

### ***Raltegravir***

RAL is FDA-approved for treatment of **infants and children** weighing  $\geq 2$  kg and can be used starting at birth. It is available in film-coated tablets, chewable tablets, and single 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 the [Antiretroviral Management of Newborns](#) section.**

#### Recommendation:

- Based on randomized clinical trials in adults and pediatric studies that were performed largely in ARV-experienced children and adolescents,<sup>7,20-26</sup> the Panel recommends RAL as a *Preferred* INSTI in **infants and children from birth** to age  $< 6$  years. **The Panel acknowledges that data regarding the efficacy of this agent in those aged  $< 2$  years are currently very limited.**<sup>27</sup>
- **Although the current FDA label includes an increased dose of RAL that can be given once-daily, the Panel does not recommend once-daily dosing for initial therapy in children and infants at this time.**

## **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 an FDA-approved pediatric indication for

treatment of HIV infection. The advantages of NNRTIs as initial therapy include 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 compared to PIs. The major disadvantages of NNRTI drugs that are FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance (except ETR) and cross-resistance to other NNRTIs is common. Rare, but serious and potentially life-threatening, skin and hepatic toxicity can occur with all NNRTI drugs, but this AE is most frequently observed with NVP, at least in 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 NNRTIs. See [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information for each drug.)

### ***Efavirenz***

EFV, when used in combination with two NRTIs, is **an *Alternative*** NNRTI for initial therapy in children aged  $\geq 3$  years to 12 years. This designation is based on clinical trial experience in adults and children. In children aged  $\geq 3$  months weighing  $\geq 3.5$  kg, EFV capsules can be opened and sprinkled on age-appropriate food.<sup>28</sup> However, because of concerns regarding variable PK of the drug in very young patients, the Panel does not currently endorse its use for infants and children aged 3 months to 3 years.

#### Recommendation:

- Based on efficacy and tolerability,<sup>13,20,28-46</sup> the Panel recommends EFV used in combination with a two-NRTI backbone as an *Alternative* NNRTI regimen for initial treatment of HIV in children aged  $\geq 3$  years (**AI\***).

### ***Nevirapine***

NVP has extensive clinical and safety experience in children with HIV and has shown ARV efficacy in a variety of combination regimens.<sup>1,5,6,47-51</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. Although there is information about the safety and PKs of NVP when it is used at doses for prophylaxis that target lower NVP drug levels than those obtained with treatment doses, there is less information regarding the higher doses necessary for treatment. Early testing of infants allows HIV infection to be confirmed before 14 days of age. In these cases, the Panel recommends the use of NVP as a *Preferred* NNRTI if treatment initiation is planned 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 outcome compared to starting after age 14 days. Consultation with an expert in pediatric HIV infection should be sought. Additional considerations regarding the use of NVP in infants aged  $< 14$  days can be found in [Antiretroviral Management of Newborns](#).

#### Recommendation:

- Based on the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare (but potentially life-threatening) instances of hepatitis,<sup>52,53</sup> and conflicting data about virologic efficacy compared to preferred regimens,<sup>1,5,6,49-51,54-63</sup> the Panel recommends NVP used in combination with a two-NRTI backbone as a *Preferred* NNRTI regimen in infants aged  $< 14$  days and an *Alternative* NNRTI regimen for children aged  $\geq 14$  days to  $< 3$  years (**AI**). A change from NVP to LPV/r should be considered after 14 days of life and 42 weeks post-gestational age based on infant genotype and the better outcomes of LPV/r in children aged  $< 3$  years.

### ***Rilpivirine***

RPV is currently available both as a single-agent formulation and a once-daily, fixed-dose combination tablet containing FTC and TDF. The single-agent formulation is approved for use in adolescents aged  $\geq 12$  years.

#### Recommendation:

- Based on the limited experience with RPV in adolescents and the larger body of evidence in adults,<sup>36,64-68</sup> the Panel recommends RPV used in combination with a two-NRTI backbone as an *Alternative* NNRTI

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\*).

## Protease Inhibitor-Based Regimens

Advantages of PI-based regimens include excellent virologic potency and high barrier for development of drug resistance (since resistance requires multiple mutations). However, because PIs are metabolized via hepatic enzymes, the drugs have 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, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly toxicities related to metabolic complications), age of the child, and availability of data in children. (Table 8 lists the advantages and disadvantages of PIs. See Appendix A: [Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.)

RTV is a potent inhibitor of the CYP450 3A4 isoenzyme and can be used in low doses as a PK booster when co-administered 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. When RTV is used as a PI booster with other PIs, two agents must be administered. In addition, the use of RTV boosting increases the potential for hyperlipidemia<sup>69</sup> and drug-drug interactions.

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

### *Atazanavir/Ritonavir*

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 (ATV/r). Approval was extended in 2014 for use in infants and children aged  $\geq 3$  months and weighing  $\geq 5$  kg. ATV in combination with COBI has been approved by the FDA for use in adults. The use of this combination in children and adolescents is under investigation, but no data are currently available.

#### Recommendation:

- Based on virologic potency observed in adult and pediatric studies and tolerability seen in pediatric studies,<sup>23,32,66,69-75</sup> the Panel recommends ATV/r used in combination with a two-NRTI backbone as a *Preferred* PI regimen for children aged  $\geq 3$  years (AI\*).
- Because of the limited experience with ATV/r in younger children, the Panel recommends ATV/r as *Alternative* PI therapy in infants and children aged  $>3$  months to  $<3$  years and weighing between 5 and 25 kg (AI\*).
- The Panel **does not recommend** unboosted ATV.

### *Darunavir/Ritonavir*

Darunavir/ritonavir (DRV/r) is FDA-approved for ARV-naïve and ARV-experienced adults and for ARV-naïve and ARV-experienced children aged  $\geq 3$  years. DRV/r is approved for once-daily use in adults and children 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>76</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. Because of the lack of efficacy data on once-daily DRV/r in treatment-naïve or treatment-experienced children aged  $<12$  years, the Panel recommends dosing DRV/r twice daily in children aged  $>3$  years to  $<12$  years.<sup>77</sup>

#### Recommendation:

- Based on the virologic potency shown by DRV/r in adult and pediatric studies, and this combination's

high barrier to development of drug resistance and excellent toxicity profile in adults and children,<sup>23,77-84</sup> the Panel recommends DRV/r used in combination with a two-NRTI backbone as a *Preferred* PI regimen for children aged  $\geq 3$  years to  $< 6$  years and children and adolescents aged  $\geq 12$  years (**AI\***).

- Based on findings from the DIONE study, once-daily dosing of DRV/r is part of a *Preferred* PI regimen in treatment-naïve children and adolescents weighing  $\geq 40$  kg (**AI\***).
- Twice-daily dosing of DRV/r is part of a *Preferred* PI regimen in children aged  $\geq 3$  to  $< 6$  years and weighing  $\geq 10$  kg and an *Alternative* PI regimen in children aged  $\geq 6$  years to  $< 12$  years (**AI\***).
- Twice-daily dosing of DRV/r should be used if the following DRV resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

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

LPV/r is approved for treatment of HIV infection in adults and in infants and children with a postmenstrual age  $\geq 42$  weeks and postnatal age  $\geq 14$  days. Once-daily LPV/r is FDA-approved for initial therapy in adults,<sup>85</sup> but PK data in children do not support a recommendation for once-daily dosing.<sup>86-88</sup>

#### Recommendation:

- Based on the virologic potency observed in adult and pediatric studies and the tolerability seen in pediatric studies,<sup>13,34,70,71,78,85-87,89-93</sup> the Panel recommends LPV/r used in combination with a two-NRTI backbone as a *Preferred* PI regimen for infants with a postmenstrual age  $\geq 42$  weeks and postnatal age  $\geq 14$  days to  $< 3$  years (**AI**).
- LPV/r, in combination with a two-NRTI backbone, is recommended as an *Alternative* PI regimen in children aged  $\geq 3$  years.

## **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 FDA-approved 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; and TAF used in combination with FTC.<sup>18,42,72,94-98</sup> **The Panel no longer recommends ddI or d4T as part of ARV regimens for children due to the significant toxicities observed with these drugs and the availability of safer agents.** Advantages and disadvantages of different dual-NRTI backbone options recommended for initial therapy are delineated in [Table 8](#). See [What Not to Start](#) for more information. Also, see [Appendix A: Pediatric Antiretroviral Drug Information](#) for detailed pediatric information on each drug.

In the dual-NRTI regimens listed below, 3TC and FTC are interchangeable. Both 3TC and FTC are well tolerated and have few AEs. Although there is less experience in children with FTC than with 3TC, 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 or 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 based on decreased viral fitness.<sup>99,100</sup>

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

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

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



### Recommendations:

- Based on virologic efficacy and favorable toxicity profile,<sup>21,101-108</sup> the Panel recommends ABC plus 3TC or FTC as the *Preferred* dual-NRTI combination for children aged  $\geq 3$  months (**AI**).
- Once-daily dosing of ABC is recommended when using the pill formulation. Twice-daily dosing of liquid ABC is recommended for initial therapy; a change to once-daily dosing can be considered in clinically stable patients with undetectable viral loads and stable CD4 cell counts after approximately 6 months (24 weeks) of twice-daily dosing.<sup>109-112</sup>

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

TAF is an oral prodrug of tenofovir. It is approved by the FDA as a component of the fixed-dose combination tablet that also contains EVG, COBI, and FTC for the treatment of HIV in ARV-naïve 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 fixed-dose combination tablet.<sup>19</sup> A fixed-dose combination that contains just FTC/TAF (Descovy) is also available.

### Recommendation:

- Based on the potential for less renal and bone AEs with TAF when compared to TDF,<sup>16,113</sup> the Panel recommends FTC/TAF as a *Preferred* dual-NRTI combination in children and adolescents aged  $\geq 6$  years who have estimated CrCl  $\geq 30$  mL/min when this combination is used as FTC/TAF with an INSTI or NNRTI. This combination is recommended as an *Alternative* drug combination when used in the single-tablet regimen EVG/COBI/FTC/TAF for children aged  $\geq 6$  years to  $< 12$  years and weighing  $\geq 25$  kg to  $< 35$  kg.
- For children and adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg, FTC/TAF is recommended as a *Preferred* drug combination when used in the single-tablet regimen EVG/COBI/FTC/TAF or as FTC/TAF used in combination with an NNRTI, INSTI, or a boosted PI.
- FTC/TAF is neither FDA approved 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.

### **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 licensed for treatment in infants aged  $\geq 4$  weeks and prophylaxis in newborns.

### Recommendation:

- Because of the extensive experience and favorable safety profile,<sup>106,114-116</sup> the Panel recommends ZDV used in combination with 3TC or FTC as a *Preferred* NRTI for infants and children from birth to age  $\leq 6$  years (**AI\***).
- In children aged  $\geq 6$  years and adolescents, the Panel recommends ZDV used in combination with 3TC or FTC as an *Alternative* NRTI because ZDV must be administered twice daily.

### ***Alternative Dual-Nucleoside Reverse Transcriptase Inhibitor Regimens***

Other dual-NRTI regimens have been studied in children, and the Panel recommends the following as alternative dual-NRTI combinations.

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

TDF is FDA-approved for use in children and adolescents aged  $\geq 2$  years when administered as part of an ART regimen. Decreases in bone mineral density (BMD) have been observed in adults and children receiving TDF, but the clinical significance of these decreases is unknown.<sup>95-98,117,118</sup> The potential risks of decreased BMD versus benefits of therapy should be considered.

Recommendation:

- Based on virologic efficacy and ease of dosing,<sup>95-98,102-105,119-124</sup> the Panel recommends TDF used in combination with 3TC or FTC as an *Alternative* dual-NRTI combination for children aged  $\geq 2$  years (AI\*).

**Zidovudine in Combination with Abacavir and Zidovudine in Combination with Lamivudine or Emtricitabine**

ZDV plus ABC and ZDV plus 3TC had lower rates of viral suppression and more toxicity leading to drug modification than did ABC plus 3TC in a European pediatric study.<sup>94,101</sup>

Recommendation:

- The Panel recommends ZDV in combination with ABC as an *Alternative* dual-NRTI combination for use in children  $\geq 3$  months (BII).
- In children aged  $\geq 6$  years and adolescents who are not sexually mature (SMR 1–3), the Panel recommends ZDV used in combination with 3TC or FTC as an *Alternative* dual NRTI combination (BII).

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

An ART regimen for treatment-naïve children generally contains one NNRTI or one PI boosted with RTV or COBI or one INSTI plus a two-NRTI backbone. *Preferred* regimens are designated based on efficacy, ease of administration, and acceptable toxicity. *Alternative* regimens have also demonstrated efficacy, but have more limited experience in children or less favorable ease of administration than *Preferred* regimens. Regimens should be individualized based on the advantages and disadvantages of each combination (see Table 8).

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

Preferred Regimens		
Age	Regimens	Fixed-Dose Combination Available
Infants, Birth to Age <14 Days <sup>a,b</sup>	2 NRTIs <b>plus</b> NVP	No
	2 NRTIs <b>plus</b> RAL	No
Children Aged $\geq 14$ Days to <3 Years	2 NRTIs <b>plus</b> LPV/r	No
	2 NRTIs <b>plus</b> RAL <sup>c</sup>	No
Children Aged $\geq 3$ Years to <6 Years	2 NRTIs <b>plus</b> ATV/r	No
	2 NRTIs <b>plus</b> twice-daily DRV/r <sup>d</sup>	No
	2 NRTIs <b>plus</b> RAL <sup>c</sup>	No
Children Aged $\geq 6$ Years to <12 Years	2 NRTIs <b>plus</b> ATV/r	No
	2 NRTIs <b>plus</b> DTG <sup>e</sup>	No
Adolescents Aged $\geq 12$ Years and SMR 1–3	2 NRTIs <b>plus</b> ATV/r	No
	2 NRTIs <b>plus</b> DTG <sup>e</sup>	FDC available
	2 NRTIs <b>plus</b> once-daily DRV/r <sup>d</sup>	No
	2 NRTIs <b>plus</b> EVG/COBI <sup>f</sup>	FDCs available
Adolescents Aged $\geq 12$ Years and SMR 4 or 5	Refer to the <a href="#">Adult and Adolescent Guidelines</a>	No
Alternative Regimens		
Age	Regimens	Fixed-Dose Combination Available
Children Aged >14 Days to <3 Years	2 NRTIs <b>plus</b> NVP <sup>g</sup>	No
Children Aged $\geq 3$ Months to <3 Years and Weighing $\geq 10$ kg	2 NRTIs <b>plus</b> ATV/r	No

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

Age	Regimens	Fixed-Dose Combination Available
Children Aged ≥3 Years to <6 Years	2 NRTIs <b>plus</b> EFV <sup>h</sup>	No
	2 NRTIs <b>plus</b> LPV/r	No
Children Aged ≥6 Years to <12 Years	2 NRTIs <b>plus</b> twice-daily DRV/r <sup>d</sup>	No
	2 NRTIs <b>plus</b> EFV <sup>h</sup>	No
	2 NRTIs <b>plus</b> EVG/COBI <sup>f</sup>	FDCs available
	2 NRTIs <b>plus</b> LPV/r	No
	2 NRTIs <b>plus</b> RAL <sup>c</sup>	No
Adolescents Aged ≥12 Years and SMR 1–3	2 NRTIs <b>plus</b> EFV <sup>h</sup>	FDC available
	2 NRTIs <b>plus</b> RAL <sup>c</sup>	No
	2 NRTIs <b>plus</b> RPV <sup>i</sup>	FDC available
<b>Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs</b>		
Age	2-NRTI Backbone Options	Fixed-Dose Combination Available
Children, Birth to Age <3 Months	ZDV <b>plus</b> (3TC <b>or</b> FTC) <sup>j</sup>	No
Children Aged ≥3 Months to <6 Years	ABC <b>plus</b> (3TC <b>or</b> FTC) <sup>k</sup>	FDC available
	ZDV <b>plus</b> (3TC <b>or</b> FTC) <sup>j</sup>	FDC available
Children and Adolescents Aged ≥6 Years and SMR 1–3	ABC <b>plus</b> (3TC <b>or</b> FTC) <sup>k</sup>	FDC available
	FTC/TAF <sup>l</sup>	FDC available
Adolescents Aged ≥12 Years and SMR 4 or 5	Refer to the <a href="#">Adult and Adolescent Guidelines</a>	No
<b>Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs</b>		
Age	2-NRTI Backbone Options	Fixed-Dose Combination 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>m</sup>	FDC available
Children and Adolescents Aged ≥6 Years and SMR 1–3	ZDV <b>plus</b> (3TC <b>or</b> FTC) <sup>j</sup>	FDC available

<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. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Clinicians should consult an expert in pediatric HIV infection. Additional considerations regarding the use of NVP **or** RAL in infants aged <14 days can be found in [Antiretroviral Management of Newborns](#). A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth), based on infant genotype and better outcomes of LPV/r than NVP in children aged <3 years. Data are very limited on the clinical outcomes of using RAL in infants and children aged <2 years.

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

<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.

<sup>d</sup> DRV once daily should not be used in children aged <12 years or weighing <40 kg. DRV once daily should also not be used if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is an *Alternative* recommendation for children aged ≥6 years to <12 years because there are options that can be administered once daily. It is *Preferred* for adolescents aged ≥12 years who are not sexually mature (SMR 1–3) where once-daily administration is possible.

<sup>e</sup> DTG is recommended only for children and adolescents weighing ≥30 kg. An FDC tablet containing ABC/DTG/3TC (Triumeq) is available.

<sup>f</sup> EVG is currently recommended only in FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as *Preferred* for children

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

and adolescents weighing  $\geq 35$  kg and as *Alternative* for children aged  $\geq 6$  years and weighing  $\geq 25$  kg.

<sup>g</sup> NVP should not be used in postpubertal girls with CD4 cell counts  $>250/\text{mm}^3$ , unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged  $\geq 15$  days.

<sup>h</sup> EFV is licensed for use in children aged  $\geq 3$  months and weighing  $\geq 3.5$  kg, but it is not recommended by the Panel as initial therapy in children aged  $\geq 3$  months to 3 years. An FDC tablet containing EFV/FTC/TDF (Atripla) is available.

<sup>i</sup> RPV should be administered to adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg who have an initial viral load  $\leq 100,000$  copies/mL. FDC tablets containing FTC/RPV/TAF (Odefsey) and FTC/RPV/TDF (Complera) are available.

<sup>j</sup> An FDC containing 3TC/ZDV (Combivir and generic) is available.

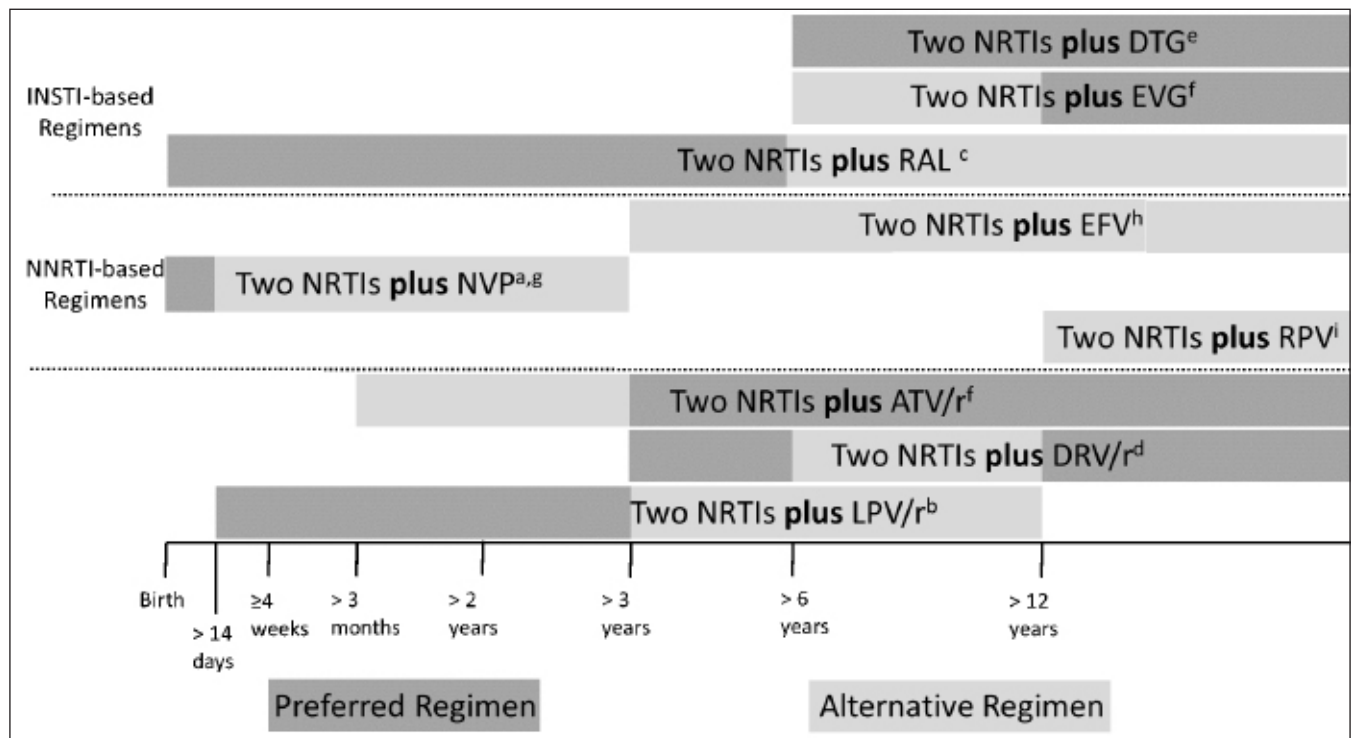
<sup>k</sup> An FDC containing ABC/3TC (Epzicom and generic) is available.

<sup>l</sup> An FDC containing FTC/TAF is available. FTC/TAF is FDA-approved for children weighing  $\geq 25$  kg when used in the single-tablet regimen EVG/COBI/FTC/TAF or as TAF/FTC in combination with an NNRTI or INSTI. There is insufficient data to recommend use of FTC/TAF in combination with a boosted PI in children weighing  $<35$  kg. For children and adolescents weighing  $\geq 35$  kg, TAF can be used in the single-tablet regimen EVG/COBI/FTC/TAF, or as FTC/TAF in combination with an NNRTI, an INSTI, or a boosted PI.

<sup>m</sup> An FDC containing FTC/TDF (Truvada) is available.

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

**Figure 2. Preferred and Alternative Regimens by Age and Drug Class**



<sup>a</sup> If treatment is scheduled to begin before a patient is aged 14 days, NVP or RAL are the *Preferred* agents because they are the only options with dosing information available for this age group. However, there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome (compared with starting after 14 days of age). Clinicians should consult an expert in pediatric HIV infection. Additional considerations regarding the use of NVP or RAL in infants aged  $<14$  days can be found in [Antiretroviral Management of Newborns](#). A change from NVP to LPV/r should be considered when the infant is aged  $\geq 14$  days and 42 weeks postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth), based on infant genotype and better outcomes of LPV/r than NVP in children aged  $<3$  years. Data are

## Figure 2. Preferred and Alternative Regimens by Age and Drug Class, continued

very limited on the clinical outcomes of using RAL in infants and children aged <2 years.

- <sup>b</sup> LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and postnatal age  $\geq 14$  days.
- <sup>c</sup> RAL pills or chewable tablets can be used in children aged  $\geq 2$  years. Granules can be administered in infants and children from birth to age 2 years.
- <sup>d</sup> DRV once daily should not be used in children aged <12 years or weighing <40 kg. DRV once daily should also not be used if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. DRV/r is an *Alternative* recommendation for children aged  $\geq 6$  years to <12 years because there are options that can be administered once daily. It is preferred for adolescents aged  $\geq 12$  years and SMR 1–3 where once-daily administration is possible.
- <sup>e</sup> DTG is recommended only for children and adolescents weighing  $\geq 30$  kg. For those children weighing <30 kg, RAL can be considered if an INSTI-based regimen is desired.
- <sup>f</sup> EVG is currently recommended only in FDC tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as *Preferred* for children and adolescents weighing  $\geq 35$  kg and *Alternative* for children and adolescents weighing  $\geq 25$  kg.
- <sup>g</sup> NVP should not be used in post-pubertal girls with CD4 cell counts  $>250/\text{mm}^3$ , unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged  $\geq 15$  days.
- <sup>h</sup> EFV is licensed for use in children aged  $\geq 3$  months and weighing  $\geq 3.5$  kg but is not recommended by the Panel as initial therapy in children aged  $\geq 3$  months to 3 years.
- <sup>i</sup> RPV should be administered to adolescents aged  $\geq 12$  years and weighing  $\geq 35$  kg who have an initial viral load  $\leq 100,000$  copies/mL.

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

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order	All INSTIs	<u>INSTI Class Advantages:</u> <ul style="list-style-type: none"> <li>• Susceptibility of HIV to a new class of ARV drugs</li> <li>• Few drug-drug interactions</li> <li>• Well-tolerated</li> </ul>	<u>INSTI Class Disadvantages:</u> <ul style="list-style-type: none"> <li>• Limited data on pediatric dosing or safety</li> </ul>
	DTG	<ul style="list-style-type: none"> <li>• Once-daily administration</li> <li>• Can give with food</li> <li>• Available in an FDC tablet containing ABC/DTG/3TC (Triumeq) in a single, but large, tablet</li> <li>• Single-agent DTG pills are available in several dosages and are small in size.</li> </ul>	<ul style="list-style-type: none"> <li>• Drug interactions with EFV, FPV/r, TPV/r, and rifampin, necessitating twice-daily dosing</li> <li>• CNS side effects, particularly sleep disturbances</li> </ul>
	EVG	<ul style="list-style-type: none"> <li>• Once-daily administration</li> <li>• Available in the following FDC tablets: EVG/COBI/FTC/TDF (Stribild) and EVG/COBI/FTC/TAF (Genvoya)</li> </ul>	<ul style="list-style-type: none"> <li>• COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4).</li> <li>• COBI inhibits tubular secretion of creatinine and may result in increased serum creatinine but normal glomerular clearance.</li> </ul>
	RAL	<ul style="list-style-type: none"> <li>• Can give with food</li> <li>• Available in tablet, chewable tablet, and powder formulations</li> <li>• Once-daily administration (with RAL HD) can be used for treatment-naïve or virologically suppressed children weighing <math>\geq 50</math> kg.</li> </ul>	<ul style="list-style-type: none"> <li>• Potential for rare systemic allergic reaction or hepatitis</li> <li>• Powder formulation requires a multistep preparation before administration.</li> </ul>

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

<b>ARV Class</b>	<b>ARV Agent(s)</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>NNRTIs</b> In Alphabetical Order	All NNRTIs	<u>NNRTI Class Advantages:</u> <ul style="list-style-type: none"> <li>• Long half-life</li> <li>• Less dyslipidemia and fat maldistribution than PIs</li> <li>• PI-sparing</li> <li>• Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens</li> </ul>	<u>NNRTI Class Disadvantages:</u> <ul style="list-style-type: none"> <li>• 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 with all NNRTIs (but highest with NVP )</li> <li>• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)</li> </ul>
	EFV	<ul style="list-style-type: none"> <li>• Once-daily administration</li> <li>• Available in the FDC EFV/FTC/TDF (Atripla)</li> <li>• Potent ARV activity</li> <li>• Can give with food (but avoid high-fat meals)</li> <li>• Capsules can be opened and added to food</li> </ul>	<ul style="list-style-type: none"> <li>• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects)</li> <li>• Rash (generally mild)</li> <li>• No commercially available liquid</li> <li>• Limited data on dosing for children aged &lt;3 years</li> <li>• No data on dosing for children aged &lt;3 months</li> </ul>
	NVP	<ul style="list-style-type: none"> <li>• Liquid formulation available</li> <li>• Dosing information for young infants available</li> <li>• Can give with food</li> <li>• Extended-release formulation is available that allows for once-daily dosing in older children.</li> </ul>	<ul style="list-style-type: none"> <li>• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen</li> <li>• Higher incidence of rash/HSR than other NNRTIs</li> <li>• Higher rates of serious hepatic toxicity than EFV</li> <li>• Decreased virologic response compared with EFV</li> <li>• Twice-daily dosing necessary in children with BSA &lt;0.58 m<sup>2</sup></li> </ul>
	RPV	<ul style="list-style-type: none"> <li>• Once-daily dosing</li> <li>• Available in the following 1-pill-daily, FDC tablets: FTC/RPV/TDF (Complera) and FTC/RPV/TAF (Odefsey)</li> </ul>	<ul style="list-style-type: none"> <li>• Should not use in patients with HIV viral load &gt;100,000 copies/mL</li> <li>• Low barrier for resistance</li> </ul>
<b>PIs</b> In Alphabetical Order	All PIs	<u>PI Class Advantages:</u> <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 containing a PI targets HIV at 2 steps of viral replication by inhibiting the activity of viral reverse transcriptase and protease enzymes.</li> </ul>	<u>PI Class Disadvantages:</u> <ul style="list-style-type: none"> <li>• Metabolic complications, including dyslipidemia, fat maldistribution, 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- or NNRTI-based regimens for patients taking solid formulations</li> <li>• Poor palatability of liquid preparations, which may affect adherence to treatment regimen</li> <li>• Most PIs require RTV boosting, resulting in associated drug interactions.</li> </ul>

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

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order, continued	Boosted ATV	<ul style="list-style-type: none"> <li>Once-daily dosing</li> <li>Powder formulation available</li> <li>ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).</li> <li>ATV requires a boosting agent. ATV/COBI is available as an FDC tablet (Evotaz), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of ATV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for ATV that is FDA-approved for use in children.</li> </ul>	<ul style="list-style-type: none"> <li>No liquid formulation</li> <li>Food effect (should be administered with food)</li> <li>Indirect hyperbilirubinemia is common, but asymptomatic</li> <li>Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG)</li> <li>RTV component associated with a large number of drug interactions</li> </ul>
	Boosted DRV	<ul style="list-style-type: none"> <li>Can be used once daily in children aged <math>\geq 12</math> years</li> <li>Liquid formulation available</li> <li>DRV requires a boosting agent. DRV/COBI is available as an FDC tablet (Prezcobix), which can reduce the pill burden associated with a boosted-PI regimen. However, the use of DRV/COBI in pediatric patients is still being investigated. RTV is currently the only boosting agent for DRV that is FDA-approved for use in children.</li> </ul>	<ul style="list-style-type: none"> <li>Pediatric pill burden high with current tablet dose formulations</li> <li>Food effect (should be administered with food)</li> <li>Must be boosted to achieve adequate plasma concentrations</li> <li>Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown.</li> <li>RTV component associated with a large number of drug interactions</li> <li>Can only be used once daily in the absence of certain PI-associated resistance mutations</li> </ul>
	LPV/r	<ul style="list-style-type: none"> <li>LPV only available coformulated with RTV in liquid and tablet formulations.</li> <li>Tablets can be given without regard to food, but may be better tolerated when taken with meal or snack.</li> </ul>	<ul style="list-style-type: none"> <li>Poor palatability of liquid formulation (bitter taste), although palatability of combination is better than RTV alone</li> <li>Food effect (liquid formulation should be administered with food)</li> <li>RTV component is associated with large number of drug interactions</li> <li>Should not be administered to neonates before a postmenstrual age (the span of time between the first day of the mother's last menstrual period and birth, plus the time elapsed after birth) of 42 weeks and a postnatal age <math>\geq 14</math> days</li> <li>Must be used with caution in patients with pre-existing conduction system defects (can prolong PR and QT interval of ECG)</li> </ul>
Dual-NRTI Backbones In Alphabetical Order	ABC plus (3TC or FTC)	<ul style="list-style-type: none"> <li>Palatable liquid formulations</li> <li>Can give with food.</li> <li>ABC and 3TC are available in the following FDC tablets: ABC/3TC (Epzicom and generic; for older/larger patients) and ABC/DTG/3TC (Triumeq; a single, large tablet).</li> </ul>	<ul style="list-style-type: none"> <li>Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment.</li> </ul>
	FTC/TAF for children aged $\geq 6$ years	<ul style="list-style-type: none"> <li>Once-daily dosing</li> <li>Small tablet size</li> <li>Less TFV-associated renal and bone toxicity with TAF compared to TDF in adults</li> <li>FTC and TAF are available in the following FDC tablets: FTC/TAF (Descovy), EVG/COBI/FTC/TAF (Genvoya), and FTC/RPV/TAF (Odefsey)</li> </ul>	<ul style="list-style-type: none"> <li>Limited data in children</li> <li>Increased lipids</li> </ul>

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children<sup>a</sup>** (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 SMR 4 or 5	<ul style="list-style-type: none"> <li>• Once-daily dosing for TDF</li> <li>• Resistance is slow to develop</li> <li>• Less mitochondrial toxicity than other NRTIs</li> <li>• Can give with food</li> <li>• Available as reduced-strength tablets and oral powder for use in younger children</li> <li>• FTC and TDF are available in the following FDC tablets: FTC/TDF (Truvada; available in multiple dosages), EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and FTC/RPV/TDF (Complera)</li> </ul>	<ul style="list-style-type: none"> <li>• Limited pediatric experience</li> <li>• Potential bone and renal toxicity; toxicity may be less in post-pubertal children</li> <li>• Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents, including ddl, LPV/r, ATV, and TPV.</li> </ul>
	ZDV <b>plus</b> (3TC <b>or</b> FTC)	<ul style="list-style-type: none"> <li>• Extensive pediatric experience</li> <li>• ZDV and 3TC are coformulated as single pill (Combivir and generic) for older/larger patients.</li> <li>• Palatable liquid formulations</li> <li>• Can give with food</li> <li>• FTC is available as a palatable liquid formulation administered once daily.</li> </ul>	<ul style="list-style-type: none"> <li>• Bone marrow suppression with ZDV</li> <li>• Lipoatrophy with ZDV</li> </ul>
	ZDV <b>plus</b> ABC	<ul style="list-style-type: none"> <li>• Palatable liquid formulations</li> <li>• Can give with food</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment</li> <li>• Bone marrow suppression and lipoatrophy with ZDV</li> </ul>

<sup>a</sup> See [Appendix A: Pediatric Antiretroviral Drug Information](#) and [Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios](#) in the [Adult and Adolescent Guidelines](#) for more information.

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

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## What Not to Start: Regimens Not Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated May 22, 2018; last reviewed May 22, 2018)

Many additional antiretroviral (ARV) agents and combinations are available; some are not recommended for initial therapy, although they may be used in treatment-experienced children. This section describes ARV drugs and drug combinations that are not recommended or for which data are insufficient to recommend use for initial therapy in ARV-naive children.

### *Not Recommended*

These include drugs and drug combinations that are not recommended for initial therapy in ARV-naive children because of inferior virologic response, potential serious safety concerns (including potentially overlapping toxicities), pharmacologic antagonism, or better options within a drug class. These drugs and drug combinations are listed in [Table 9](#).

### *Insufficient Data to Recommend*

Drugs and drug combinations approved for use in adults that have insufficient, limited, and/or no pharmacokinetic (PK) or safety data for children cannot be recommended as initial therapy in children. However, these drugs and drug combinations may be appropriate to consider when managing treatment-experienced children (see [Management of Children Receiving Antiretroviral Therapy](#)). These drugs are also listed in [Table 9](#).

### *Antiretroviral Drugs and Combinations Not Recommended for Initial Therapy*

In addition to the regimens listed below, several ARV drugs, including tenofovir disoproxil fumarate (TDF) given to children aged <2 years, once-daily dosing of lopinavir/ritonavir (LPV/r), and full-dose ritonavir, are not recommended for use as initial therapy.

#### *Atazanavir without Ritonavir Boosting*

Although unboosted atazanavir is Food and Drug Administration (FDA)-approved for use in treatment-naive adolescents aged  $\geq 13$  years and weighing  $>39$  kg who are unable to tolerate ritonavir, data from the IMPAACT/PACTG 1020A study indicate that higher doses of unboosted atazanavir (on a mg/m<sup>2</sup> basis) are required in adolescents than in adults to achieve adequate drug concentrations.<sup>1</sup> The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** using atazanavir without ritonavir boosting because of these findings.

#### *Enfuvirtide-Based Regimens*

Enfuvirtide, a fusion inhibitor, is FDA-approved for use in combination with other ARV drugs to treat children aged  $\geq 6$  years who have evidence of HIV replication despite ongoing antiretroviral therapy (ART) (i.e., treatment-experienced children on non-suppressive regimens). Enfuvirtide must be administered subcutaneously twice daily and is associated with a high incidence of local injection site reactions (98%). Enfuvirtide is not recommended as initial therapy.

#### *Fosamprenavir-Based Regimens*

Fosamprenavir (the prodrug of amprenavir) is available in a pediatric liquid formulation and a tablet formulation, and has been investigated in children both with and without ritonavir boosting; it was approved by the FDA in June 2007 for use in patients aged  $\geq 2$  years.<sup>2-5</sup> Fosamprenavir-containing regimens are not recommended for initial therapy because the volume of liquid medication when administered in the suspension form (without ritonavir boosting) needed is associated with vomiting in young children. There are also more advantageous boosted-protease inhibitor (PI) agents available. In addition, low levels of exposure may result in selection of resistance mutations that are associated with darunavir resistance.

#### *Indinavir-Based Regimens*

Although adequate virologic and immunologic responses have been observed with indinavir-based regimens



in adults, the drug is not available in a liquid formulation and high rates of hematuria, sterile leukocyturia, and nephrolithiasis have been reported in pediatric patients using indinavir.<sup>6-9</sup> Therefore, indinavir used alone or with ritonavir boosting is not recommended as initial therapy in children.

### *Nelfinavir-Based Regimens*

The pediatric experience with nelfinavir-based regimens in ARV-naive and ARV-experienced children is extensive, with follow-up in children receiving the regimen continuing for as long as 7 years.<sup>10</sup> The drug has been well tolerated; diarrhea is the primary adverse effect. However, in clinical studies, the virologic potency of nelfinavir has varied greatly. The optimal dose of nelfinavir in younger children, particularly in those aged <2 years, has not been well defined. Data in adults show inferior potency of nelfinavir compared with ritonavir-boosted PIs, integrase strand transfer inhibitors (INSTIs), and efavirenz. For these reasons, the Panel does not recommend nelfinavir as initial therapy in children.

*Regimens Containing Only Nucleoside Reverse Transcriptase Inhibitors* In adult trials, regimens containing only nucleoside reverse transcriptase inhibitors (NRTIs) have shown less potent virologic activity when compared with more potent non-nucleoside reverse transcriptase inhibitor (NNRTI)- or PI-based regimens.<sup>11,12</sup> Data on the efficacy of triple-NRTI regimens for treatment of ARV-naive children are limited; in small observational studies, response rates of 47% to 50% have been reported.<sup>13,14</sup> In a study on the use of the triple-NRTI regimen abacavir, lamivudine, and zidovudine in previously treated children, the combination showed evidence of only modest viral suppression, with only 10% of 102 children maintaining viral loads of <400 copies/mL at 48 weeks of treatment.<sup>15</sup> Therefore, regimens containing only NRTIs are not recommended. A possible exception to this recommendation is the treatment of young children (aged <3 years) with concomitant HIV and tuberculosis for whom a nevirapine-based regimen is not acceptable. For these children, where treatment choices are limited, the World Health Organization recommends the use of a triple-NRTI regimen.<sup>16</sup>

### *Regimens Containing Three Drug Classes*

Data are insufficient to recommend initial regimens containing agents from three drug classes (e.g., NRTI plus NNRTI plus PI or INSTI plus NRTI plus PI/NNRTI). Although studies of regimens containing three classes of drugs have demonstrated that these regimens are safe and effective in previously treated children and adolescents, these regimens have not been studied as initial therapy in treatment-naive children and adolescents and have the potential for inducing resistance to three drug classes, which could severely limit future treatment options.<sup>17-21</sup> Ongoing studies, however, are investigating the use of three drug classes as treatment in neonates.

### *Regimens Containing Three NRTIs and an NNRTI*

Data are currently insufficient to recommend a regimen of three NRTIs plus an NNRTI in young infants. A recent review of nine cohorts from 13 European countries suggested superior responses to this four-drug regimen when compared to boosted-PI or three-drug NRTI regimens.<sup>22</sup> There has been speculation that poor tolerance and poor adherence to a PI-based regimen may account for differences. The ARROW trial, conducted in Uganda and Zimbabwe, randomized 1,206 children (median age 6 years) to receive either a standard NNRTI-based three-drug regimen or a four-drug regimen (three NRTIs and one NNRTI). After a 36-week induction period, the children on the four-drug regimen continued treatment on a dual-NRTI plus NNRTI regimen or an all-NRTI regimen. Although early benefits in CD4 T lymphocyte (CD4) improvement and virologic control were observed in the four-drug arm, these benefits were not sustained after de-intensification to the three-NRTI arm.<sup>23</sup> Furthermore, after a median of 3.7 years on therapy, children in the initial four-drug arm who changed to an all-NRTI regimen had significantly poorer virologic control.<sup>24</sup> Based on demonstrated benefits of recommended three-drug regimens and lack of additional efficacy data on the four-drug regimen, the Panel does not currently recommend this regimen.

### *Saquinavir/Ritonavir*

A saquinavir/ritonavir-based regimen demonstrated comparable virologic and immunologic outcomes to a

LPV/r-based regimen when used as initial therapy in treatment-naive adults.<sup>25</sup> However, saquinavir is not recommended for initial therapy in children because the agent is not available in a pediatric formulation, and dosing and outcome data on saquinavir use in children are limited.

#### *Tipranavir-Based Regimens*

Tipranavir has been studied in treatment-experienced children and adults. This agent is a PI licensed for use in children aged  $\geq 2$  years. Tipranavir-based regimens are not recommended because high doses of ritonavir must be used to boost tipranavir and rare, but serious, cases of intracranial hemorrhage have been reported.

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

Several ARV drugs and drug regimens are not recommended for initial therapy in ARV-naive children or for specific age groups because of insufficient pediatric data. These include the dual-NRTI backbone combinations abacavir/didanosine and abacavir/TDF. In addition, several new agents appear promising for use in adults but do not have sufficient pediatric PK and safety data to recommend their use as components of an initial therapeutic regimen in children. In addition, some dosing schedules may not be recommended in certain age groups based on 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](#).

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

Data are limited on PK of once-daily darunavir/ritonavir (DRV/r) in young children. While modeling studies identified a once-daily dosing regimen that is now FDA-approved, the Panel is concerned about the lack of efficacy data for individuals aged  $\geq 3$  to  $< 12$  years treated with once-daily DRV/r. Therefore, once-daily dosing for initial therapy is not recommended in this age group. For children aged  $\geq 3$  to  $< 12$  years, twice-daily DRV/r is a preferred PI regimen. For older children who have undetectable viral loads on twice-daily therapy with DRV/r, practitioners can consider changing to once-daily treatment to make this regimen easier to use and support adherence if no darunavir-associated resistance mutations are present.

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

Efavirenz is FDA-approved for use in children aged  $> 3$  months and weighing  $\geq 3.5$  kg. Concerns regarding variable PK of the drug in the very young have resulted in a recommendation to not use efavirenz in children aged  $< 3$  years at this time (see [Efavirenz](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)). When use of efavirenz is being considered for children aged  $< 3$  years, CYP2B6 genotyping that predicts efavirenz metabolic rate should be performed, if available. Therapeutic drug monitoring can also be considered.

#### *Etravirine-Based Regimens*

Etravirine is an NNRTI that has been studied in treatment-experienced children aged  $\geq 6$  years.<sup>26,27</sup> It is associated with multiple interactions with other ARV drugs, including tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, and unboosted PIs, and must be administered twice daily. Studies in treatment-experienced younger children are under way. It is unlikely that etravirine will be studied in treatment-naive children.

#### *Maraviroc-Based Regimens*

Maraviroc is an entry inhibitor that is FDA-approved for use in children aged  $\geq 2$  years and weighing  $\geq 10$  kg who have CCR5-tropic HIV-1 infection. It has been used infrequently in children. A dose-finding study in treatment-experienced children aged 2 to 18 years is enrolling patients in four age cohorts using both liquid and tablet formulations. Initial dose is based on body surface area and scaled from recommended adult dose. Dose adjustments were required in patients who were not receiving a potent CYP450 3A4 inhibitor or inducer.<sup>28</sup> The drug has multiple drug interactions and must be administered twice daily. In addition, tropism assays must be performed prior to use to ensure the presence of only CCR5-tropic virus.

## Antiretroviral Drug Regimens That Should Never Be Recommended

Several ARV drugs and drug regimens should never be recommended for use in therapy of children or adults. These are summarized in [Table 10](#). Clinicians should be aware of the components of fixed-dose drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination. **The Panel no longer recommends the use of didanosine or stavudine as part of any ARV regimen. Didanosine and stavudine—given individually or together—should never be used due to the significant toxicities of these drugs and the availability of safer agents. Co-administration of stavudine and didanosine in an ARV regimen is contraindicated (with no exceptions) due to the enhanced toxicity of this combination. The combination of stavudine and didanosine has been linked to cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis in women who received this combination during pregnancy.**<sup>29,30</sup>

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

Regimen or ARV Component	Rationale
Unboosted <b>ATV</b> -containing regimens in children	Reduced exposure
<b>DRV</b> -based regimens once daily in children aged $\geq 3$ to 12 years	Insufficient data to recommend
Unboosted <b>DRV</b>	Use without ritonavir has not been studied
Dual (full-dose) PI regimens	Insufficient data to recommend Potential for added toxicities
Dual-NRTI combination of <b>ABC plus TDF</b>	Insufficient data to recommend
<b>EFV</b> -based regimens for children aged $< 3$ years	Appropriate dose not determined
<b>T-20</b> -containing regimens	Insufficient data to recommend Injectable preparation
<b>ETR</b> -based regimens	Insufficient data to recommend
<b>FPV</b> -based regimens	Reduced exposure Medication burden
<b>IDV</b> -based regimens	Renal toxicities
<b>LPV/r</b> dosed once daily	Reduced drug exposure
<b>MVC</b> -based regimens	Insufficient data to recommend
<b>NFV</b> -based regimens	Variable PK Appropriate dose not determined in young infants
Regimens containing only NRTIs	Inferior virologic efficacy
Regimens containing 3 drug classes	Insufficient data to recommend
Full-dose <b>RTV</b> or use of <b>RTV</b> as the sole PI	GI intolerance Metabolic toxicity
Regimens containing 3 NRTIs and 1 NNRTI	Added cost and complexity outweighs any benefit
<b>SQV</b> -based regimens	Limited dosing and outcome data
<b>TDF</b> -containing regimens in children aged $< 2$ years	Potential bone toxicity Appropriate dose has yet to be determined
<b>TPV</b> -based regimens	Increased dose of RTV for boosting Reported cases of intracranial hemorrhage

**Key to Acronyms:** ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; DRV = darunavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; GI = gastrointestinal; IDV = indinavir; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetics; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

**Table 10. ART Regimens or Components Never Recommended for Treatment of HIV Infection in Children**

<b>ART Regimens <u>Never</u> Recommended for Children</b>		
<b>Regimen</b>	<b>Rationale</b>	<b>Exceptions</b>
<b>1 ARV Drug Alone (Monotherapy)</b>	<ul style="list-style-type: none"> <li>• Rapid development of resistance</li> <li>• Inferior antiviral activity compared to combinations that include <math>\geq 3</math> ARV drugs</li> <li>• Monotherapy “holding” regimens are associated with more rapid CD4 declines than non-suppressive ART</li> </ul>	<ul style="list-style-type: none"> <li>• Infants with perinatal HIV exposure and negative virologic tests who are receiving 4 to 6 weeks of ZDV prophylaxis to prevent perinatal transmission of HIV</li> </ul>
<b>2 NRTIs Alone</b>	<ul style="list-style-type: none"> <li>• Rapid development of resistance</li> <li>• Inferior antiviral activity compared to combinations that include <math>\geq 3</math> ARV drugs</li> </ul>	<ul style="list-style-type: none"> <li>• Not recommended for initial therapy.</li> <li>• For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment.</li> </ul>
<b>TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen</b>	<ul style="list-style-type: none"> <li>• High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>TDF plus ddI plus (3TC or FTC) as a Triple-NRTI Regimen</b>	<ul style="list-style-type: none"> <li>• High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>ARV Components <u>Never</u> Recommended as Part of an ARV Regimen for Children</b>		
<b>Regimen</b>	<b>Rationale</b>	<b>Exceptions</b>
<b>ddI and d4T, Individually or Co-Administered</b>	<ul style="list-style-type: none"> <li>• Increased toxicities</li> <li>• ddI plus d4T is <b>contraindicated</b></li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>ATV plus IDV</b>	<ul style="list-style-type: none"> <li>• Potential additive hyperbilirubinemia</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>Dual-NNRTI Combinations</b>	<ul style="list-style-type: none"> <li>• Enhanced toxicity</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<b>Dual-NRTI Combinations:</b>	<ul style="list-style-type: none"> <li>• Similar resistance profile and no additive benefit</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
• <b>3TC plus FTC</b>		
• <b>d4T plus ZDV</b>	<ul style="list-style-type: none"> <li>• Antagonistic effect on HIV</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>
<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>	<ul style="list-style-type: none"> <li>• Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups</li> </ul>	<ul style="list-style-type: none"> <li>• Only if benefit clearly outweighs risk</li> </ul>
<b>Unboosted SQV, DRV, or TPV</b>	<ul style="list-style-type: none"> <li>• Poor oral bioavailability</li> <li>• Inferior virologic activity compared with other PIs</li> </ul>	<ul style="list-style-type: none"> <li>• No exceptions</li> </ul>

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

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# Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last updated September 21, 2018; last reviewed November 15, 2017)

## Panel's Recommendations

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

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

**Rating of Evidence:** I = One or more randomized trials 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

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

All newborns exposed to HIV should receive antiretroviral (ARV) drugs in the neonatal period to reduce perinatal transmission of HIV, with selection of the appropriate type of ARV regimen guided by the

**level of transmission risk.** The most important contributors to the risk of HIV transmission to a newborn exposed to HIV are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. The risk of transmission is increased in the absence of maternal ART or if maternal antepartum/intrapartum treatment was started after early pregnancy or was ineffective in producing virologic suppression; higher maternal viral load, especially in later pregnancy, correlates with higher risk of transmission. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status. **Also, HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.**

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

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

It is noteworthy that, with the important exception of nevirapine, the neonatal ARV dosing for prophylaxis is the same as that for treatment for all ARV drugs currently recommended for newborns. **The terms ARV prophylaxis and empiric HIV therapy describe the clinician's intent in prescribing ARV drugs. At this time, the only difference between ARV prophylaxis containing three ARV drugs and empiric HIV therapy would be the dosage of nevirapine. As newer agents are available for use in newborns, additional differences will emerge.** The interval during which newborn ARV prophylaxis **or empiric HIV therapy** can be initiated and still be of benefit is undefined; however, most studies support providing prophylaxis as early as possible after delivery.<sup>1-6</sup>

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



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

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

Category	Description	Neonatal ARV Management
<b>Low Risk of Perinatal HIV Transmission</b>	Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence	4 weeks of ZDV
<b>Higher Risk of Perinatal HIV Transmission<sup>a,b</sup></b>	<ul style="list-style-type: none"> <li>Mothers who received neither antepartum nor intrapartum ARV drugs</li> <li>Mothers who received only intrapartum ARV drugs</li> <li>Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal</li> <li>Mothers with acute or primary HIV infection during pregnancy or breastfeeding<sup>c</sup></li> </ul>	Combination ARV prophylaxis with 6 weeks ZDV and 3 doses of NVP (prophylaxis dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose) or Empiric HIV therapy consisting of ZDV, 3TC, and NVP (treatment dosage) <sup>d</sup>
<b>Presumed Newborn HIV Exposure</b>	Mothers with unknown HIV status who test positive at delivery or postpartum or whose newborns have a positive HIV antibody test	ARV management as above (for higher risk of perinatal HIV transmission). ARV management should be discontinued immediately if supplemental testing confirms that mother does not have HIV.
<b>Newborn with Confirmed HIV<sup>e</sup></b>	Confirmed positive newborn HIV virologic test/NAT	3 drug combination ARV regimen at treatment dosage

<sup>a</sup> See text for evidence supporting combination ARV prophylaxis and empiric HIV therapy.

<sup>b</sup> See the [Intrapartum Care](#) section for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with elevated viral load at delivery.

<sup>c</sup> Most experts would opt to administer empiric HIV therapy to infants with acute HIV during pregnancy because of the high risk for *in utero* infection. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.

<sup>d</sup> The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue NVP and/or 3TC after the return of negative newborn testing. ZDV should be continued for 6 weeks.

<sup>e</sup> Most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing.

**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 8 for dosing specifics.

**Key to Acronyms:** 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; ZDV = zidovudine

**Table 12. Newborn Antiretroviral Dosing Recommendations**

Drug	Dosing								
<p><b>ZDV</b> Treatment and Prophylaxis Dosage</p> <p><b>Note:</b> For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.</p>	<p><u>≥35 Weeks' Gestation at Birth</u> <i>Birth to Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 4 mg/kg/dose orally twice daily</li> </ul> <p><b>Simplified Weight-Band Dosing for Newborns ≥35 Weeks:</b></p> <table border="1" data-bbox="578 384 1253 617"> <thead> <tr> <th data-bbox="578 384 902 491">Weight Band (kg)</th> <th data-bbox="909 384 1253 491">* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th> </tr> </thead> <tbody> <tr> <td data-bbox="578 491 902 533">2 to &lt;3 kg</td> <td data-bbox="909 491 1253 533">1 mL</td> </tr> <tr> <td data-bbox="578 533 902 575">3 to &lt;4 kg</td> <td data-bbox="909 533 1253 575">1.5 mL</td> </tr> <tr> <td data-bbox="578 575 902 617">4 to &lt;5 kg</td> <td data-bbox="909 575 1253 617">2 mL</td> </tr> </tbody> </table> <p><u>≥30 to &lt;35 Weeks' Gestation at Birth</u> <i>Birth–Age 2 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 2 Weeks to 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 3 mg/kg/dose orally twice daily</li> </ul> <p><u>&lt;30 weeks' Gestation at Birth</u> <i>Birth–Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 3 mg/kg/dose orally twice daily</li> </ul>	Weight Band (kg)	* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily	2 to <3 kg	1 mL	3 to <4 kg	1.5 mL	4 to <5 kg	2 mL
Weight Band (kg)	* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily								
2 to <3 kg	1 mL								
3 to <4 kg	1.5 mL								
4 to <5 kg	2 mL								
<p><b>3TC</b> Treatment and Prophylaxis Dosage</p>	<p><u>≥32 Weeks' Gestation at Birth:</u> <i>Birth–Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 4 mg/kg/dose orally twice daily</li> </ul>								
<p><b>NVP</b> Prophylaxis Dosage</p>	<p><u>≥32 Weeks Gestation at Birth:</u> 3 doses given (1) within 48 hours of birth, (2) 48 hours after the 1st dose, and (3) 96 hours after the 2nd dose</p> <p><u>Birth Weight 1.5–2 kg:</u></p> <ul style="list-style-type: none"> <li>• 8-mg dose orally</li> <li>• <b>Note:</b> No calculation is required for this dose; <b>this is the actual dose, not a mg/kg dose.</b></li> </ul> <p><u>Birth Weight &gt;2 kg:</u></p> <ul style="list-style-type: none"> <li>• 12-mg dose orally</li> <li>• <b>Note:</b> No calculation is required for this dose; <b>this is the actual dose, not a mg/kg dose.</b></li> </ul>								
<p><b>NVP</b> Treatment Dosage</p>	<p><u>≥37 Weeks' Gestation at Birth</u> <i>Birth–Age 6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 6 mg/kg/dose orally twice daily</li> </ul> <p><u>34 to &lt;37 Weeks' Gestation at Birth</u> <i>Birth–Age 1 Week:</i></p> <ul style="list-style-type: none"> <li>• 4 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 1–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 6 mg/kg/dose orally twice daily</li> </ul>								

**Key to Acronyms:** 3TC=lamivudine; IV= intravenous; NVP = nevirapine; ZDV = zidovudine

## ***Recommendations for Antiretrovirals in Specific Clinical Situations***

In the following sections and Table 11, we present available data and recommendations for management of **newborns with confirmed HIV** and newborns born to mothers who:

- Received antepartum/intrapartum ARV drugs with effective viral suppression
- Are at higher risk of transmitting HIV to their newborn, including those who:
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs
  - Received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal
- Have acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

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

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

Therefore, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends a 4-week neonatal zidovudine prophylaxis regimen for newborns if the mother has received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) near delivery and there are no concerns related to maternal adherence. Dosing recommendations for zidovudine are available for premature newborns and an intravenous preparation is available. [Table 12](#) shows recommended neonatal zidovudine dosing based on gestational age and birthweight.

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

All newborns born to mothers with detectable viral load at the time of delivery, who received only intrapartum ARV drugs, or who have received no ARV drugs during pregnancy or delivery, are at higher risk of HIV acquisition and should receive combination ARV prophylaxis **or empiric HIV therapy**.<sup>5,10-14</sup> **The experience with combination ARV prophylaxis and empiric HIV therapy is described below. At this time, the optimal duration of combination ARV regimens or empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of negative newborn testing but continue zidovudine for 6 weeks.**

For those women who received ARV drugs during pregnancy, but have a detectable viral load near delivery, the level of viremia in the mother that would trigger the use of combination newborn prophylaxis is not definitively known. In 2 large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had viral load measurements <50 copies/mL at delivery. Rates of transmission increased to 1.1% and 1.5% when viral load measurements were 50 to 399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.<sup>15,16</sup> However, there has been no study to demonstrate relative efficacy of combination **ARV regimens, including prophylaxis regimens and empiric HIV therapy**, compared to standard newborn prophylaxis at these different thresholds of maternal viremia. While some experts would recommend a combination ARV regimen or empiric HIV therapy with any level of detectable viremia, others reserve combination regimens and empiric HIV therapy until higher levels of maternal viral load are documented. The decision to administer a combination prophylaxis regimen or empiric therapy should be made following discussion with the parents weighing the risks and benefits of **the proposed regimen**.

**Primary or acute HIV infection during pregnancy is associated with an increased risk of perinatal transmission of HIV. Combination ARV prophylaxis or empiric HIV therapy should be administered to the infant until HIV can be confirmed or ruled out. (see [Acute HIV Infection](#)).**

**In summary, in these scenarios where the infant is at higher risk of HIV transmission, the Panel recommends either combination ARV prophylaxis or empiric HIV therapy. The data supporting the use of combination ARV prophylaxis regimens and empiric HIV therapy are summarized below. Choosing between combination ARV prophylaxis and empiric HIV treatment will depend on the clinician assessment of the likelihood of HIV transmission.**

### **Combination Antiretroviral Prophylaxis**

There is a paucity of data from randomized clinical trials to guide the optimal selection of a newborn combination prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of combination prophylaxis in newborns at high risk of HIV acquisition. In this study, 1,746 formula-fed newborns born to women with HIV who did not receive any ARV drugs during pregnancy were randomized to 1 of 3 newborn prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. Forty-one percent of mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone;  $P = .046$  for each experimental arm vs. zidovudine alone).<sup>5</sup> **The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in 3/53 (5.7%) participants with *in utero* infection who were treated with zidovudine alone and in 6/33 (18.2%) participants treated with zidovudine plus nevirapine ( $P > 0.05$ ). In addition, the third drug in the three-arm regimen was nelfinavir, which has highly variable kinetics in this age group and did not reach the kinetic target in 46% of study participants.<sup>17</sup> Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or zidovudine-alone regimen (27.5% vs. 15%,  $P < 0.0001$ ).**

Data from Europe and the United States indicate increasing use of combination ARV prophylaxis in newborns exposed to HIV. In the United Kingdom and Ireland, use increased from 9% of newborns exposed to HIV in 2001 to 2004 to 13% between 2005 to 2008 and, in a poll of 134 U.S.-based providers, 62% reported using combination prophylaxis in high-risk newborns.<sup>18-20</sup> However, interpretation of these observational studies is complicated by the definition of combination ARV prophylaxis, **use of prophylaxis versus treatment dosing of nevirapine**, and combining heterogeneous combination ARV prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many studies include single-dose nevirapine in combination with another ARV, usually zidovudine, as combination therapy. Most do not report whether nevirapine was administered at the **recommended** prophylaxis dose or at a higher dose **as part of empiric HIV therapy**. So,

despite increasing utilization of various combination ARV prophylaxis regimens, comprehensive data on efficacy and safety are lacking. Therefore, based on the NICHD-HPTN 040/PACTG 1043 trial, the 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine is the combination ARV prophylaxis regimen recommended by the Panel for newborns at higher risk of HIV acquisition ([Tables 11](#) and [12](#)).

### **Empiric HIV Therapy**

A three-drug ARV regimen including zidovudine, lamivudine, and the treatment dose of nevirapine (**empiric HIV therapy**) is the other option recommended by the Panel for newborns at high risk of HIV acquisition.

Enthusiasm for this approach followed a case of a “functional cure” of HIV in a newborn reported in 2013.<sup>21</sup> The newborn was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and was diagnosed as having HIV by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. At age 30 hours, the newborn initiated a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher treatment dose rather than standard prophylactic dosing). The newborn was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these tests, the newborn was continued on treatment for HIV, thought to be acquired *in utero*. At age 18 months, the mother discontinued ART; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for over 2 years without ART. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest, another case of virologic rebound following 4 years of suppression in a newborn treated since birth has subsequently been reported.<sup>22</sup>

Further support of empiric HIV therapy comes from Canadian investigators who have reported outcomes in 136 newborns considered at high risk of HIV acquisition (i.e., born to women with HIV who had detectable viral load and/or poor adherence to therapy prior to delivery) who received a triple-ARV regimen within 72 hours of birth. Of these 136 newborns, 12 (9%) were found to have acquired HIV and no major toxicities were identified.<sup>23</sup> However, there was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug regimens. Another Canadian study compared the safety of empiric HIV therapy in 148 newborns with high-risk exposure (i.e., incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) and 145 control low-risk newborns who received only zidovudine. Thirteen newborns in the empiric HIV therapy group acquired HIV, including 5 with a positive HIV nucleic acid test (NAT) within the first 48 hours of life, suggesting *in utero* infection. No newborn in the low-risk zidovudine-only group acquired HIV. The newborns receiving empiric HIV therapy demonstrated more non-specific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects compared to none of the newborns receiving zidovudine only (10.2% vs. 0%,  $P < 0.001$ ). ARV drugs were also more likely to be discontinued prematurely in the newborns receiving empiric HIV therapy (9.5% vs. 2.1%,  $P = 0.01$ ).<sup>24</sup>

Empiric HIV therapy in newborns is consistent with the Centers for Disease Control and Prevention recommendations for occupational and non-occupational post-exposure prophylaxis in adults, where risk of infection is often lower than in newborns at high risk of HIV acquisition.<sup>25,26</sup> However, there are two key safety issues related to the choice and dose of ARV drugs in these newborns. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels at least 10-fold lower than targeted therapeutic levels. The optimal dose for empiric HIV therapy in newborns has not been sufficiently studied but studies are ongoing. Second, lopinavir/ritonavir is not recommended for neonates younger than age 14 days because of the potential for significant toxicity (see [Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis](#)). Therefore, the risks of empiric HIV therapy in terms of newborn toxicity (particularly in preterm newborns) and efficacy require further study before a general recommendation can be made.

There are three ongoing clinical trials investigating newborn empiric HIV therapy containing nevirapine at

treatment doses, zidovudine, and lamivudine shortly after birth in newborns at high risk of HIV infection (international multisite IMPAACT P1115, ClinicalTrials.gov identifier NCT02140255), or those known to have HIV (BHP-074 in Botswana, NCT02369406, and the Leopard Study in South Africa, NCT02431975). Additional safety and pharmacokinetic (PK) data from these studies will guide future recommendations.

At this time, if an empiric HIV therapy regimen is selected, the Panel recommends a combination of zidovudine, lamivudine, and nevirapine (treatment dosage) (see [Tables 11 and 12](#)). The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of a negative newborn testing. Zidovudine should be continued for 6 weeks.

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

Expedited HIV testing of mothers is recommended during labor for women with unknown HIV status and for mothers and/or newborns as soon as possible after birth if expedited HIV testing was not performed during labor (see [Identification of Perinatal Exposure](#)). Expedited test results should be available within 60 minutes. If expedited testing is positive, newborn combination ARV prophylaxis or empiric HIV therapy should be initiated immediately, without waiting for the results of supplemental tests as described below. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care, special care or newborn nursery.

A positive initial test result in mothers or newborns should be presumed to indicate maternal HIV until standard supplemental testing clarifies maternal and newborn status. If appropriate test results on a mother (or newborn) are negative, newborn ARV drugs can be discontinued. Clinicians should be aware of their state laws, as there is variability in the testing allowed without parental consent.

Breastfeeding should be stopped until HIV is confirmed or ruled out in a woman who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result. 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>27</sup>

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

The optimal ARV regimen for newborns delivered by women with ARV drug-resistant virus is unknown. It is also unknown whether resistant virus in the mother increases the risk of HIV acquisition by the infant. The ARV regimen for newborns born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery or through consultation with the [National Perinatal HIV Hotline](#) (888-448-8765). However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Data from the WITS study suggest that, in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted.<sup>28,29</sup> Thus, the selection of the newborn ARV regimen should be based on other risk factors ([Table 11](#)).

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.<sup>29</sup> However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.<sup>30-34</sup>

### **Newborns with Confirmed HIV**

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT testing results meant that neonatal infections were generally not diagnosed in the first weeks of life. HIV NAT test results now often are available within a few days and newborns with HIV are being diagnosed as early as the first days of life. A positive HIV NAT

test must be repeated to confirm HIV. However, most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing. However, evidence that very early treatment (before age 2 weeks) will produce a prolonged remission or lead to better outcomes in newborns with HIV is lacking. Earlier diagnosis of HIV in newborns and the increasing use of empiric HIV therapy in newborns at high risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same with the important exception of nevirapine (see [Pediatric Antiretroviral Drug Information](#)).

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

- From birth in term and preterm newborns: [zidovudine](#), [lamivudine](#), [nevirapine](#)
- From birth in term neonates: [emtricitabine](#), [raltegravir](#)
- From age 2 weeks in term neonates: [lopinavir/ritonavir](#)

Dosing recommendations for *premature* newborns are available for only zidovudine, [lamivudine](#), and nevirapine. Neonatal dosing advice, including for premature newborns, is summarized in Table 8. For more detailed information about neonatal dosing recommendations and considerations of these drugs, please see the [Pediatric Antiretroviral Drug Information](#) for these drugs.

### **Newborns of Mothers Diagnosed with HIV while Breastfeeding**

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding is not recommended for women with confirmed HIV in the United States, including those receiving ART (see [Newborn Feeding Practices and Risk of HIV Transmission](#)).<sup>35</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>36</sup> Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than are those whose mothers have chronic HIV infection<sup>37</sup> because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.<sup>38</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 experts 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 compared with other non-occupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure.<sup>39</sup>

Several studies of newborns breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn nevirapine, lamivudine, lopinavir/ritonavir or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.<sup>40-44</sup> **No trials have evaluated the use of combination regimens for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection.**

Because of the high risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some experts would be to offer empiric HIV therapy until infant status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of empiric HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational

HIV exposure.<sup>39</sup> As in other situations, decisions regarding ARV management should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach. The [National Perinatal HIV Hotline](#) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Newborns should be tested for HIV **prior to initiation of** empiric HIV therapy and 4 to 6 weeks, 3 months, and 6 months after recognition of maternal HIV and cessation of breastfeeding to determine HIV status. (see [Diagnosis](#) section). If a newborn is already receiving an ARV prophylaxis regimen other than empiric HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV initiated. Resistance testing should be performed, and the ART regimen modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

### ***Short-Term Antiretroviral Drug Safety***

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

Other than zidovudine, lamivudine is the NRTI with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 113,45,46 or 2 weeks.<sup>5</sup> Six weeks of newborn zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the newborns also had in utero exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in newborns exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and newborn zidovudine. Anemia was reported in 15% and neutropenia in 18% of newborns exposed to zidovudine/lamivudine, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.<sup>47</sup> Similarly, in a Brazilian study of maternal antepartum and 6-week newborn zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of newborns.<sup>48</sup>

Experience with other NRTI drugs for neonatal prophylaxis is more limited.<sup>49,50</sup> Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.<sup>47,51-54</sup>

In rare cases, chronic multiple-dose nevirapine prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.<sup>55</sup> These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding newborns receiving nevirapine prophylaxis daily for 6 weeks to **18** months to prevent transmission of HIV via breast milk.<sup>5,40-42,44,56</sup>

Of the protease inhibitors, pediatric drug formulations are available for lopinavir/ritonavir, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended due to lack of dosing and safety information. In addition, lopinavir/ritonavir oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (2 sets of twins) started on lopinavir/ritonavir from birth, developed heart block that resolved after drug discontinuation.<sup>57,58</sup> In studies of adults, both ritonavir and lopinavir/ritonavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of lopinavir/ritonavir compared with zidovudine in the neonatal period. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to lopinavir/ritonavir in utero compared with those exposed



only in the neonatal period. Term newborns were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.<sup>59</sup> Based on 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>60</sup> predominantly in preterm neonates, the U.S. Food and Drug Administration (FDA) now recommends that lopinavir/ritonavir oral solution **not** be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.<sup>61</sup> However, a recent study (ANRS 12174) randomized 1,273 newborns, 615 assigned to lopinavir/ritonavir and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life and only newborns greater than 2 kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that lopinavir/ritonavir is safe in term newborns, 7 days of age and older.<sup>62</sup> At this time, the Panel does not recommend the use of lopinavir/ritonavir before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

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## Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV (Last updated May 22, 2018; last reviewed May 22, 2018)

### Panel's Recommendations

- All adolescents should receive maximally suppressive antiretroviral therapy (ART); this is urgent for those who are sexually active, considering pregnancy, or pregnant (AII).
- ART selection should consider the adolescent's individual needs and preferences (AIII).
- Reproductive health issues, including pregnancy intentions, contraceptive methods, safer sex techniques to prevent transmission of HIV and other sexually transmitted infections, pre-exposure prophylaxis (PrEP) for partners, pregnancy planning, and preconception care should be discussed regularly (AI).
- Providers should be aware of potential interactions between ART and hormonal contraceptives that could lower contraceptive efficacy (AII\*).
- Pediatric and adolescent care providers should prepare adolescents for the transition into adult care settings (AIII).

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

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

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

## Background

The majority of individuals in the United States who acquired HIV through perinatal transmission are now adolescents or young adults; only about 16% are aged <13 years.<sup>1</sup> Most have had a long clinical course with an extensive history of treatment with antiretroviral therapy (ART).<sup>2,3</sup> Many older youth and adults initially received nonsuppressive mono- or dual-therapy prior to the availability of combination regimens. Challenges that affect the treatment of adolescents with perinatally acquired HIV include extensive drug resistance, complex regimens, the long-term consequences of HIV and ART exposure,<sup>4</sup> social determinants, and psychosocial factors.<sup>5-8</sup>

Most post-pubertal adolescents living with HIV in the United States acquired their infection by horizontal, rather than perinatal, transmission. They generally follow a clinical course similar to that of adults and the [Adult and Adolescent Guidelines](#) should be used for treatment recommendations.<sup>9</sup>

## 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 (PK), which is especially important for medications (e.g., the protease inhibitor [PI] atazanavir) that have a narrow therapeutic index and that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.<sup>10</sup>

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some PIs) are administered to children at higher body weight- 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. The choice of some ARVs, specifically TDF, is based on sexual maturity rating (SMR, formerly Tanner staging) and not on age, due to concerns about associated toxicity.

## Timing and Selection of Antiretroviral Therapy

All individuals who are living with HIV, including adolescents, should initiate ART promptly. Optimal dosing recommendations for initial therapy that are pertinent to adolescents whose SMRs are between 1 and 3 are available in [Appendix A: Pediatric Antiretroviral Drug Information](#) and [What to Start](#). Recommendations for initial therapy for adolescents and young adults whose SMRs are between 4 and 5 are available in the [What to Start](#) section of the [Adult and Adolescent Guidelines](#). These recommendations reflect results from two key randomized controlled trials in adults (START and TEMPRANO), which both demonstrated that the clinical benefits of ART are greater when ART is started early, when a patient's pre-treatment CD4 T lymphocyte (CD4) count is  $>500$  cells/mm<sup>3</sup>, than when ART is initiated at a lower CD4 cell count threshold.<sup>11,12</sup>

## Adherence Concerns in Adolescents

Adolescents living with HIV are especially vulnerable to adherence problems resulting from their psychosocial and cognitive developmental trajectory. Comprehensive systems of care are required to serve both the medical and psychosocial needs of adolescents living with HIV, who are frequently inexperienced with personally managing health care systems and may lack health insurance. Compared with adults, these 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 Guidelines](#) and a review by Agwu and Fairlie.<sup>4</sup>

A specific challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternatives to initiating or changing ARV therapy can include, **but are not limited to**: reminders to the patient through cell phone alerts, a short-term deferral of treatment until adherence is improved or while adherence-related problems are aggressively addressed, an adherence testing and training period in which a placebo (e.g., vitamin pill) is administered, **more frequent appointments, directly observed therapy**, and the avoidance of any regimens with a low genetic resistance threshold. Such decisions should be individualized, and the patient's clinical and laboratory status should be monitored carefully.

## Sexually Transmitted Infections in Adolescents

Sexually transmitted infections (STIs), including human papilloma virus (HPV), should be addressed in all adolescents. 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>16</sup> **For all adolescents, there should be a detailed sexual history (to elicit practices that may place them at increased risk for STI acquisition) and to inform appropriate screening.** For a more detailed discussion of STIs, see the most recent Centers for Disease Control and Prevention guidelines<sup>17</sup> **and the [Human Papillomavirus Disease section in the \[Adult and Adolescent Opportunistic Infections Guidelines\]\(#\) and the \[Human Papillomavirus section in the \\[Pediatric Opportunistic Infections Guidelines\\]\\(#\\).\]\(#\)](#)**<sup>18,19</sup> All female adolescents living with HIV who are sexually active should receive gynecologic care, and all adolescents should be immunized with the HPV vaccination.

## Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents living with HIV may initiate sexual activity before or after puberty. **Sexually active adolescents are at risk for unintended pregnancy. Data indicate that approximately half of pregnancies in the United States, including those among women with HIV, are unintended or unplanned.**<sup>20,21</sup> **Providers should regularly assess adolescents' desires to become pregnant or avoid pregnancy (fertility intentions).** Family planning counseling, including a discussion of the risks of **sexual HIV transmission**, perinatal HIV transmission, and methods for reducing these risks, should be provided to all youth. Reproductive health options, such as pregnancy planning, preconception care, contraception methods, and safer sex techniques (including instruction on the correct and consistent use of condoms) for prevention of secondary HIV transmission,

should be discussed regularly (see [U.S. Medical Eligibility Criteria for Contraceptive Use](#)).<sup>22</sup> For additional information, readers are referred to sections of the Perinatal Guidelines entitled [Preconception Counseling and Care for Women of Childbearing Age Living with HIV](#) and [Reproductive Options for Couples with the Same or Differing HIV Status](#).<sup>23</sup> [The American Academy of Pediatrics Committee on Adolescence offers guidance about the integration of sexual and reproductive health care in pediatric clinical settings.](#)<sup>24</sup>

The possibility of planned and unplanned pregnancy should be considered when selecting an ART regimen for an adolescent female. The most vulnerable period in fetal organogenesis is the first trimester, often before pregnancy is recognized. Concerns about specific ARV drugs and birth defects should be promptly addressed (for additional information please see the [Teratogenicity section](#) of the [Perinatal Guidelines](#)).<sup>23</sup> Readers should consult 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](#).

### ***Contraceptive-Antiretroviral Drug Interactions***

Women living with HIV can use all available contraceptive methods, including [hormonal contraceptives](#), [implantable devices](#), [intrauterine devices](#), the transdermal patch, and vaginal ring.<sup>23</sup>

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs alter the metabolism of oral contraceptives, which theoretically may reduce the efficacy of oral contraceptive agents or increase the risk of estrogen- or progestin-related adverse effects (see the [Adult and Adolescent Guidelines](#) and the [HIV Drug Interaction Checker](#)).<sup>25-27</sup> Integrase strand transfer inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives.<sup>28</sup> For more information about potential interactions between ARVs and hormonal contraceptives, please see [Table 3](#) in the [Perinatal Guidelines](#).

Concerns about loss of bone mineral density (BMD) with long-term use of depot medroxyprogesterone acetate (DMPA), with or without ART (specifically TDF), should not preclude use of DMPA as an effective contraceptive, unless there is clinical evidence of bone fragility. However, monitoring of BMD in young women on DMPA should be considered.<sup>29</sup>

### ***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 for use of ART during pregnancy (see the [Perinatal Guidelines](#)).<sup>23</sup> Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of perinatal transmission and maternal and fetal safety, selection of regimens may be different for pregnant women or women planning to become pregnant than for nonpregnant women. See the [Perinatal Guidelines](#)<sup>23</sup> for more details about choosing an ART regimen for pregnant women living with HIV, including adolescents. Pregnancies are currently being reported as girls with perinatally acquired HIV enter adolescence and young adulthood.<sup>30,31</sup> Some studies suggest higher rates of adverse pregnancy outcomes, such as small-for-gestational-age infants, among pregnant women with perinatal infection than among those with horizontal infection, and unplanned pregnancy appears frequent.<sup>31-33</sup> However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV who are receiving ART appears similar to that among women on ART who acquired HIV by horizontal transmission.<sup>34-38</sup>

### **Transition of Adolescents into Adult HIV Care Settings**

Facilitating a seamless transition for adolescents living with HIV from their pediatric/adolescent medical home to adult care is important but challenging.<sup>39</sup> Pediatric and adolescent providers and their multidisciplinary teams should have a formal written plan in place to transition adolescents to adult care. While transition generally occurs when individuals are in their late teens or early 20s, [discussion of and](#) [planning for the](#) transition process should be initiated early in the second decade of life [with involvement from both the adolescent and his or her parents and/or caregivers](#). Transition is “a multifaceted, active



process that attends to the medical, psychosocial, cognitive and educational, or vocational needs of adolescents as they move from the child-focused to the adult-focused health care system.”<sup>40</sup> Care models for children and adolescents with perinatal HIV tend to be family-centered, consisting of a multidisciplinary team that often includes pediatric or adolescent 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, an adolescent may be unfamiliar with the more individual-centered, busier clinics typical of adult medical providers and may be uncomfortable with providers with whom they do not have a long-standing relationship. Providing adolescents and their new adult medical care providers with support and guidance regarding the expectations for each partner in the patient-provider relationship may be beneficial. In this situation, it may be helpful for a pediatric and an adult provider to share joint care of a patient for a period of time.

The adolescent-care provider should have a candid discussion with the transitioning adolescent to understand what qualities the adolescent considers most important in choosing an adult care setting (e.g., confidentiality, small clinic size, **low patient-to-provider ratio**, availability of after-school **or evening** appointments). Additional factors that should be considered during transition include social determinants, such as developmental status, behavioral/mental health issues, housing, family support, employment status, recent discharge from foster care, peer pressure, illicit drug use, and incarceration. Psychiatric comorbidities and their effective management predict adherence to medical care and therapy.<sup>41-44</sup>

Currently, there is no definitive model of transition to adult HIV care and only a limited number of reports about outcomes following transition, **though research in this area is ongoing**. In some studies, youth followed into adult care settings have had higher rates of attrition from care than those remaining 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.<sup>15</sup> A report from the United Kingdom suggests an increased risk of mortality after transition.<sup>43</sup> In a report from a Baltimore clinic on 50 youth (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>45</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 to 19 years. These rates decreased to 76% and 58% for those aged 20 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>3</sup> **A recent retrospective study from Atlanta reported that, while retention rates were initially high once adolescents entered adult care, they had declined significantly by the second year after transition. Pretransition viral suppression and shorter linkage time between the pediatric and adult clinic were associated with better outcomes post-transition.**<sup>46</sup>

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transitional plans and who might benefit most from them.<sup>47-54</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:

- Developing a written, individualized transition plan to address comprehensive care needs, including medical, psychosocial, and financial aspects of transitioning;
- Optimizing provider communication between pediatric/adolescent clinics and adult clinics;
- Identifying adult care providers who have expertise in providing care to adolescents and young adults;
- Addressing patient or family barriers caused by lack of information, stigma or disclosure concerns, and differences in practice styles;
- Preparing youth for life skills development, 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 self-efficacy in managing medications, insurance, and state and federal benefits;

- Identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in);
- Clearly defining the desired outcomes for the transition, such as retention in care, ongoing access to other services (e.g., case management, mental health), clinical outcomes (e.g., viral suppression), and patient satisfaction;
- Implementing ongoing evaluations to measure the success of a selected 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;
- Incorporating a family-planning component into clinical care;
- Educating HIV care teams and staff about transitioning; and
- Beginning discussions regarding transition early, before the actual transition process.

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# Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV (Last updated May 22, 2018; last reviewed May 22, 2018)

## Panel's Recommendations

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

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

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

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

## Background

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

Poor adherence to ARV drugs is commonly encountered in the treatment of children and adolescents living with HIV. A variety of factors—including medication formulation, frequency of dosing, drug toxicities and side effects, child's age and developmental stage, as well as psychosocial, behavioral, and sociodemographic characteristics of children and caregivers—have been associated with nonadherence. However, no consistent predictors of either good or poor adherence in children have been consistently identified.<sup>4-6</sup> Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.<sup>7</sup> These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to work in partnership 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 patient-provider relationship.<sup>8,9</sup> The limited availability of once-daily and single-tablet regimens and palatable formulations for infants and young children is especially problematic.<sup>10</sup> Furthermore, infants and children are dependent on others for medication administration; barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal.<sup>11,12</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>13</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, involvement with the criminal justice system, limited social support).<sup>14</sup>

## Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A comprehensive assessment should be instituted for all children in whom ART initiation or change is considered. Evaluations should assess social and behavioral factors that may influence adherence by children and their families and should identify individual needs for intervention. Specific, open-ended questions should be used to elicit information about experience **with taking medications**, as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain a patient's explicit agreement with the treatment plan, including strategies to support adherence. It is also important to alert patients to potential adverse effects of ARV drugs (e.g., nausea, headaches, abdominal discomfort, **sleep disturbances**), explain how they can be managed, and emphasize the importance of informing the clinical team if they should 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>15-18</sup> Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals on ART (see [Plasma HIV-1 RNA \[Viral Load\] and CD4 Count Monitoring](#) in the [Adult and Adolescent Guidelines](#)). In addition, it can be used as positive reinforcement to encourage continued adherence.<sup>19</sup> Clinicians should use at least one other method to assess adherence in addition to monitoring viral load.<sup>17,20</sup> [Table 13](#) includes commonly employed approaches to monitoring medication adherence.

## Strategies to Improve and Support Adherence

Intensive follow-up is required, particularly during the first few months after therapy is initiated or changed. If there are concerns about adherence, patients should be seen and/or contacted (by phone, text messaging, email, and social networking, as allowed within the context of local legal and regulatory requirements) frequently—as often as weekly, or even more often, during the first month of treatment—to assess adherence and determine the need for strategies to improve and support adherence.

Strategies should include simplifying the drug regimen, developing treatment plans that accommodate specific patient needs to 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—rather than one specific intervention—may be most effective.<sup>13,21,22</sup> The evidence is mixed as to the efficacy of programs designed for the administration of directly observed therapy (DOT) to improve adherence, but DOT may still be a useful strategy for some patients.<sup>21,23-27</sup>

[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>28</sup>

### *Regimen-Related Strategies*

ARV drug regimens for children often require taking multiple pills or unpalatable liquids, each with potential adverse effects (AEs) and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and AEs.<sup>29</sup> Efforts should be made to reduce the pill burden **and pill size** and to prescribe once-daily ARV drug regimens and single-tablet regimens whenever feasible (see [Management of Children Receiving Antiretroviral Therapy](#)). With the introduction of new drug

classes and a wider array of once-daily formulations, including some medications now available in small pill size, there are now more options to offer less toxic, simplified regimens, particularly for older children and adolescents. Several studies in adults have demonstrated better adherence with once-daily versus twice-daily ARV drug regimens and with single-tablet formulations compared with multiple-tablet regimens.<sup>10,30</sup>

When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste can sometimes be masked with a small amount of flavoring syrup or food (see [Appendix A: Pediatric Antiretroviral Drug Information](#)).<sup>31</sup> Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children aged 4 to 21 years found that training children to swallow pills has been associated with improved adherence at 6 months post-training.<sup>32</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, drug regimen) when feasible.

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

The primary approach to promote medication adherence in children is patient and caregiver education. Educating families about adherence should begin before ARV medications are initiated or changed and should include a discussion of the goals of therapy, the importance of optimizing adherence, and the specific plans for supporting and maintaining a child's medication adherence. Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

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>33</sup> Availability of mental health services and the treatment of mental health disorders (such as depression) may facilitate adherence to complex ARV drug regimens.<sup>34</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 exploring 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>35</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, a gastrostomy tube may be considered.<sup>36</sup> If adequate resources are available, home-nursing interventions or DOT may also be beneficial.

Other strategies to support adherence include **mobile applications (apps) that remind patients to take medications**; setting patients' cell phone alarms to go off at medication times; sending SMS text-message reminders; conducting motivational interviews; providing pill boxes, blister packaging, and other adherence support tools; and delivering medications to the home. **CDC has an adherence toolbox, which includes a free mobile app (CDC Every Dose Every Day mobile app) available through their website.** Randomized clinical trials in adults have demonstrated that text messaging is associated with improved adherence<sup>37-41</sup> and a study in poorly adherent HIV-positive adolescents and young adults demonstrated that two-way personalized daily text messaging improved self-reported adherence.<sup>42</sup> It should be noted, however, that the evidence base for effective adherence interventions in adolescents and young adults taking daily ART is limited.<sup>43-47</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. Evidence-Based 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 quantitative self-report of missed doses.	Ask patient and/or caregiver about the number of missed doses over defined period (1, 3, or 7 days).
Elicit description of medication regimen.	Ask patient and/or caregiver about the name/appearance, number, frequency of medications.
Assess barriers to medication administration.	Engage the patient and caregiver in dialogue around facilitators and challenges to adherence.
Monitor pharmacy refills.	Approaches include pharmacy-based or clinic-based assessment of on-time medication refills.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to clinic or home visits, or referral to community health nursing.
<b>Targeted Approaches to Monitor Adherence in Special Circumstances</b>	<b>Description</b>
Implement DOT.	Include brief hospitalization if indicated.
Measure plasma drug concentration.	Can be considered for particular drugs. <sup>b</sup>
<b>Approaches to Monitor Medication Adherence in Research Settings</b>	<b>Description</b>
Measure drug concentrations in hair.	Good measure of adherence over time. <sup>c</sup>
Use electronic monitoring devices.	MEMS caps, Wisepill
Use mobile phone-based technologies.	Interactive voice response, SMS text messaging, <b>mobile apps</b>

<sup>a</sup> See [Clinical and Laboratory Monitoring After Initiation of Combination Antiretroviral Therapy \(or After a Change in Combination Antiretroviral Therapy\)](#) regarding the frequency of adherence assessment after initiating or changing therapy.

<sup>b</sup> See [Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection](#) regarding indications for therapeutic drug monitoring.

<sup>c</sup> Sources:

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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>.<sup>49</sup>

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>.<sup>18</sup>

**Key to Acronyms:** apps = applications; DOT = directly observed therapy; MEMS = Medication Event Monitoring System

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

Initial Intervention Strategies
• Establish trust and identify mutually acceptable goals for care.
• Obtain explicit agreement on the need for treatment and adherence.
• Identify depression, low self-esteem, substance abuse, or other mental health issues in the child/adolescent and/or caregiver that may decrease adherence. Evaluate and initiate treatment for mental health issues before starting ARV drugs, if possible.
• Identify family, friends, health team members, and others who can support adherence.
• Educate patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and potential impact on future drug regimen choices. Develop a treatment plan that the patient and family understand and to which they feel committed.
• Work with the patient and family to make specific plans for taking medications as prescribed and supporting adherence. Assist them to arrange for administration in day care, school, and other settings, when needed. Consider home delivery of medications.
• Establish readiness to take medication through practice sessions or other means.
• Schedule a home visit to review medications and determine how they will be administered in the home setting.
• In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess tolerability of medications chosen.
Medication Strategies
• Choose the simplest regimen possible, reducing dosing frequency, pill size, and number of pills.
• When choosing a regimen, consider the daily and weekly routines and variations in patient and family activities.
• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).
• Choose drugs with the fewest AEs; provide anticipatory guidance for management of AEs.
• Simplify food requirements for medication administration.
• Prescribe drugs carefully to avoid adverse drug-drug interactions.
• Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed.
Follow-up Intervention Strategies
• Have more than one member of the multidisciplinary team monitor adherence at each visit and in between visits by telephone, email, text, and social media, as needed.
• Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.
• Use patient education aids including pictures, calendars, and stickers.
• Encourage use of pill boxes, reminders, mobile apps, alarms, and timers.
• Provide follow-up clinic visits, telephone calls, and text messages to support and assess adherence.
• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.
• Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.
• Consider DOT at home, in the clinic, or in certain circumstances, such as during a brief inpatient hospitalization.
• Consider gastrostomy tube use in certain circumstances.
• Information on other interventions to consider can be found at the <a href="#">Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions</a> .
• Consult the <a href="#">CDC Every Dose Every Day toolkit</a>

**Key to Acronyms:** apps = applications; ARV = antiretroviral; AE = adverse effect; DOT = directly observed therapy

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# Management of Medication Toxicity or Intolerance (Last updated May 22, 2018; last reviewed May 22, 2018)

## 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, antiretroviral therapy should be resumed with substitution of a different ARV drug or drugs for the offending agent(s) (**AII\***).
- When modifying therapy because of toxicity or intolerance to a specific drug in children with virologic suppression, changing one drug in a multidrug regimen is permissible; if possible, an agent with a different toxicity and side-effect profile should be chosen (**AI\***).
- The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient should be advised of the drug-related toxicity (**AIII**).
- In general, dose reduction is not a recommended option for management of ARV toxicity (**AII\***).

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

**Rating of Evidence:** I = One or more randomized trials in children<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

## Medication Toxicity or Intolerance

The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects (AEs) of some antiretroviral (ARV) drugs. However, AEs have been reported with the use of all ARV drugs and—in the mid-1990s when combination ART was introduced—were among the most common reasons for switching or discontinuing therapy and for medication nonadherence (see the [Adult and Adolescent Guidelines](#)).<sup>1</sup>

Fortunately, currently recommended ARV regimens are associated with fewer serious and intolerable AEs than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials have treatment-limiting AEs.<sup>2-11</sup> 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. To achieve sustained viral suppression over a child's lifetime, both short-term and long-term ART toxicities must be anticipated. The clinician must consider potential AEs and issues with medication palatability when selecting an ARV regimen, as well as the individual child's comorbidities, concomitant medications, and prior history of drug intolerance or viral resistance.

ARV drug-related AEs can vary from mild, more common symptoms (e.g., gastrointestinal intolerance, fatigue) to infrequent, but severe and life-threatening, illness. Drug-related toxicity can be acute (occurring soon after a drug has been administered), subacute (occurring within 1 to 2 days of administration), or late (occurring after prolonged drug administration). For a few ARV medications, pharmacogenetic markers associated with risk of early toxicity have been identified, but the only such screen in routine clinical use is HLA-B\*5701 as a marker for abacavir hypersensitivity.<sup>12-14</sup> For selected children aged <3 years who require treatment with efavirenz, an additional pharmacogenetic marker, CYP2B6 genotype, should be assessed in an attempt to prevent toxicity (see [Efavirenz](#) in [Appendix A: Pediatric Antiretroviral Drug Information](#)).<sup>13-17</sup> For agents such as efavirenz, therapeutic ranges for plasma concentrations as determined by therapeutic drug monitoring (TDM) may indicate the need for dose reduction or modification of ART in patients experiencing central nervous system (CNS) AEs (see below).

The most common acute and chronic AEs associated with ARV drugs or drug classes are presented in the [Management of Medication Toxicity or Intolerance](#) tables. The tables include information on common causative drugs, estimated frequency of occurrence, timing of symptoms, risk factors, potential preventive measures, and suggested clinical management strategies. The tables also provide selected references regarding these toxicities in pediatric patients.

## Management

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

Management strategies must be individualized for each child, taking into account the severity of the toxicity, viral suppression status, and available ARV options. Clinicians should anticipate the appearance of common, self-limited AEs, and reassure patients that many AEs will resolve after the first few weeks of ART. For example, when initiating therapy with boosted protease inhibitors (PIs), many patients experience gastrointestinal AEs such as nausea, vomiting, diarrhea, and abdominal pain. Instructing patients to take PIs with food may help minimize these AEs. Some patients may require antiemetics and antidiarrheal agents for symptom management. CNS AEs are commonly encountered when initiating therapy with efavirenz. Symptoms can include dizziness, drowsiness, vivid dreams, or insomnia. Patients should be instructed to take efavirenz-containing regimens at bedtime, on an empty stomach, to help minimize these AEs. Patients should be advised that these AEs usually diminish in general within 2 to 4 weeks of initiating therapy in most people, but may persist for months in some, and may require a medication change.<sup>18-20</sup> In addition, mild rash can be ameliorated with drugs such as antihistamines. **Addressing AEs is essential, as continued use of an ARV that a patient finds intolerable may lead the patient to stop their treatment, risking viral rebound and the development of resistance.**

In patients who experience unacceptable AEs from ART, every attempt should be made to identify the offending agent and to replace the drug with another effective agent as soon as possible.<sup>21,22</sup> **For mild to moderate toxicities, changing to a drug with a different toxicity profile may be sufficient, and discontinuation of all therapy may not be required. When interrupting a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, many experts will stop the NNRTI 7 to 14 days before stopping the dual nucleoside analogue reverse transcriptase backbone, due to the long half-life of NNRTI drugs. However, patients who have a severe or life-threatening toxicity (e.g., [HSR—see Hypersensitivity Reaction, Table 151](#)) should stop all components of the drug regimen simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the AE has been determined, planning can begin for:**

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

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

When therapy is changed because of toxicity or intolerance in a patient with virologic suppression, agents with different toxicity and side-effect profiles should be chosen, when possible.<sup>23-27</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 permissible for patients whose viral loads are undetectable. However, substitution of a single active agent for a single drug in a failing multidrug regimen

(e.g., a patient with virologic failure) **is generally not recommended** because of concern for development of resistance (see [Recognizing and Managing Antiretroviral Treatment Failure in Management of Children Receiving Antiretroviral Therapy](#)).

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

To summarize, management strategies for drug intolerance include:

- Symptomatic treatment of mild to moderate transient AEs.
- Switching one drug for another drug that is active against a patient's virus (e.g., changing to abacavir for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor [INSTI] for efavirenz-related CNS symptoms).
- Using dose reduction as guided by TDM in consultation with an expert in pediatric HIV.

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**Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 3)

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><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• 1–6 days after starting LPV/r</li> </ul> <p><u>Presentation</u></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	<p>Prematurity</p> <p>Low birth weight</p> <p>Aged &lt;14 days (whether premature or term)</p>	Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days.	<p>Discontinue LPV/r; symptoms should resolve in 1–5 days.</p> <p>If needed, reintroduction of LPV/r can be considered once outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days).</p>
<b>Neuropsychiatric Symptoms and Other CNS Manifestations</b>	EFV	<p><u>Onset:</u></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 may persist in a significant proportion of patients. In one report, 37% of participants experienced persistent symptoms at 12 months and in another report, half of discontinuations occurred after 12 months.</li> </ul> <p><u>Presentation (May Include 1 or More of the Following)</u></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> </ul>	<p>Variable, depending on age, symptom, and assessment method</p> <p><u>Children:</u></p> <ul style="list-style-type: none"> <li>• 24% for any EFV-related CNS manifestations in 1 case series, with 18% of participants requiring drug discontinuation.</li> <li>• <b>11% (5/45 participants)</b> incidence of new-onset seizures reported in 1 study in children aged &lt;36 months, 2 of whom had alternative causes <b>for seizures.</b></li> <li>• Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels.</li> </ul> <p><u>Adults:</u></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> </ul>	<p>Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL</p> <p>Presence of CYP450 polymorphisms that decrease EFV metabolism and cause increased EFV serum concentrations (CYP2B6 516 TT genotype or co-carriage of CYP2B6 516 G/T and 983 T/C variants)</p> <p>Prior history of psychiatric illness or use of psychoactive drugs</p>	<p>Administer EFV on an empty stomach, preferably at bedtime.</p> <p>Prescreen for and avoid use in the presence of psychiatric illness, including depression or suicidal thoughts. Avoid concomitant use of psychoactive drugs.</p> <p>TDM can be considered in the context of a child with mild or moderate <b>EFV-associated toxicity.</b></p>	<p>If symptoms are excessive or persistent, obtain EFV trough concentration. If EFV trough concentration &gt;4 mcg/mL <b>and/or symptoms are severe,</b> strongly consider drug substitution if suitable alternative exists.</p> <p>Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).</p>

**Table 15a. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 3)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neuropsychiatric Symptoms and Other CNS Manifestations, continued	EFV, continued	<ul style="list-style-type: none"> <li>Cerebellar dysfunction (tremor, dysmetria, ataxia)</li> </ul> <p><b>Note:</b> CNS side effects such as impaired concentration, abnormal dreams, or sleep disturbances may be more difficult to assess in children.</p>	<ul style="list-style-type: none"> <li>1 case series reported 20 women with ataxia which resolved upon EFV discontinuation, but frequency was not reported.</li> </ul>			
	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><u>Presentation</u></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><u>Adults:</u></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 (mostly Grade 1). Depressive disorders of all severity grades were reported in 9% of patients, and were severe, requiring RPV discontinuation in 1% of patients.</li> </ul> <p><u>Children:</u></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 1 suicide attempt.</li> <li>Somnolence reported in 14% (5/36) of children.</li> </ul>	Prior 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><u>Presentation:</u></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><u>Children:</u></p> <ul style="list-style-type: none"> <li>Increased psychomotor activity reported in 1 child.</li> </ul> <p><u>Adults:</u></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 or 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 co-administered 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 May 22, 2018; last reviewed May 22, 2018) (page 3 of 3)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Neuropsychiatric Symptoms and Other CNS Manifestations, continued</b>	DTG	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• 7–30 days after starting DTG</li> </ul> <p><u>Presentation</u></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> </ul> <p><i>Other CNS Manifestations (Generally Mild):</i></p> <ul style="list-style-type: none"> <li>• Insomnia</li> <li>• Dizziness</li> <li>• Headache</li> </ul>	<p><u>Children:</u></p> <ul style="list-style-type: none"> <li>• CNS symptoms were uncommonly reported in early clinical experience in children and adolescents.</li> </ul> <p><u>Adults:</u></p> <ul style="list-style-type: none"> <li>• Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common and usually mild. More severe symptoms that require drug discontinuation are less common, occurring in &lt;1% patients in Phase 3 trials, but these severe symptoms are reported with increasing frequency (4% to 10%) in recent post-marketing reports.</li> </ul>	<p>Pre-existing depression or other psychiatric illness</p> <p>Higher frequency of neuropsychiatric symptoms reported when co-administered with ABC</p>	Use with caution in the presence of psychiatric illness, especially depression.	<p>For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.</p> <p>Discontinuation resulted in resolution of neuropsychiatric symptoms in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation).</p> <p>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time.</p>
<b>Intracranial Hemorrhage (ICH)</b>	TPV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• 7–513 days after starting TPV</li> </ul>	<p><u>Children:</u></p> <ul style="list-style-type: none"> <li>• No cases of ICH reported in children.</li> </ul> <p><u>Adults:</u></p> <ul style="list-style-type: none"> <li>• In premarket approval data in adults, 0.23/100 py or 0.04–0.22/100 py in a retrospective review of 2 large patient databases.</li> </ul>	Unknown; prior history of bleeding disorder or risk factors for bleeding reported for most patients in case series.	Administer TPV with caution in patients with bleeding disorder, known intracranial lesions, or recent neurosurgery.	Discontinue TPV if ICH is suspected or confirmed.

**Key to Acronyms:** ABC = abacavir; ARV = antiretroviral; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = lopinavir/ritonavir; PPI = proton pump inhibitor; py = patient years; RAL = raltegravir; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TPV = tipranavir; UGT = uridine diphosphate-glucurononyl transferase

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

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Dyslipidemia</b>	<p><u>PIs:</u></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><u>NRTIs:</u></p> <ul style="list-style-type: none"> <li>Especially d4T<sup>e</sup></li> <li>Lower incidence reported with TDF than TAF</li> </ul> <p><u>NNRTIs:</u></p> <ul style="list-style-type: none"> <li>Lower incidence reported with NVP, RVP, and ETR than EFV</li> </ul>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>As early as 2 weeks to months after beginning therapy</li> </ul> <p><u>Presentation</u></p> <p><u>PIs:</u></p> <ul style="list-style-type: none"> <li>↑LDL-C, TC, and TG</li> </ul> <p><u>NNRTIs:</u></p> <ul style="list-style-type: none"> <li>↑LDL-C, TC, and HDL-C</li> </ul> <p><u>NRTIs:</u></p> <ul style="list-style-type: none"> <li>↑LDL-C, TC, and TG</li> </ul>	<p>Reported frequency varies with specific ARV regimen, duration of ART, and specific laboratory parameters used to diagnose lipid abnormalities.</p> <p>10% to 20% in young children receiving LPV/r.</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 in EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF regimen in studies of treatment-naïve adults.</p> <p>Increase in serum lipids from baseline also noted in adolescents receiving EVG/COBI/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 CVD</p> <p>Metabolic syndrome</p> <p>Fat maldistribution</p>	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>Low-fat diet</li> <li>Exercise</li> <li>Smoking-prevention counseling</li> <li>Do not use d4T</li> </ul> <p><u>Monitoring<sup>a</sup></u></p> <p><i>Adolescents and Adults:</i></p> <ul style="list-style-type: none"> <li>Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (&gt;2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy.</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, if levels are normal, every 6–12 months. If TG or LDL-C is elevated, obtain fasting blood tests.</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, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy.</li> </ul>	<p>Assessment of additional CVD risk factors should be done in all patients. Patients living with HIV are considered to be at moderate risk of CVD.<sup>b</sup></p> <p>Counsel on lifestyle modification and dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars, particularly in cases of ↑TG, elimination of trans fat in the diet, increase in physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician.</p> <p>ART regimen changes can be considered. Discontinue d4T or substitute a PI-sparing regimen or PI-based regimen with a more favorable lipid profile.</p> <p>Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails.</p> <p>Some experts suggest treating children receiving ARV drugs according to NHLBI cardiovascular risk reduction guidelines for children aged ≥10 years: LDL-C ≥190 mg/dL, regardless of additional risk factors; LDL-C ≥160 mg/dL or LDL-C ≥130 mg/dL based on presence of additional risk factors and risk conditions.<sup>b</sup></p> <p>The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL, while minimizing side effects and maintaining viral control.</p>

**Table 15b. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia**  
 (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Dyslipidemia					<ul style="list-style-type: none"> <li>If minimal alterations in AST, ALT, and CK, monitor every 3–4 months in the first year and every 6 months thereafter (or as clinically indicated).</li> <li>Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents.</li> </ul>	<p>Statins such as pravastatin, atorvastatin, or rosuvastatin<sup>c</sup> can be considered.<sup>d</sup> <b>Pravastatin has lower lipid-lowering potency compared to other statins.</b> Statin-induced lipid lowering effect appears more pronounced than ARV substitution. Statin-related toxicities include liver enzyme elevation and myopathy, and risk may be increased by drug interactions with ART, particularly PIs.<sup>e</sup> Statins may also increase the risk of insulin resistance and <b>type 2 diabetes mellitus, but data are conflicting.</b> Risks must be weighed against potential benefits. Cholesterol absorption inhibitors (e.g., ezetimibe) can be considered as alternatives.</p> <p>Drug therapy for severe hypertriglyceridemia (TG ≥500 mg/dL) can be considered. Fibrates (gemfibrozil and fenofibrate) and N-3 PUFAs derived from fish oils may be used.</p> <p>The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD.</p>

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

<sup>b</sup> Refer to NHLBI guidelines at [https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds\\_guidelines\\_full.pdf](https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_full.pdf).

<sup>c</sup> The risks of new treatment-related toxicities and virologic failure that could occur with changes in therapy must be weighed against the potential risk of drug interactions and toxicities associated with the use of lipid-lowering agents.

<sup>d</sup> Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (due to being potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (except for pravastatin, which is not dependent on CYP3A4 for metabolism). Pravastatin, atorvastatin, rosuvastatin (Crestor®), fluvastatin, and ezetimibe (Zetia®) are approved for use in children aged ≥10 years. For additional information, see the [PI](#), [NNRTI](#), [NRTI](#), and [INSTI](#) Drug Interactions Tables in the Adult and Adolescent Guidelines.

<sup>e</sup> **d4T is no longer recommended for use in an ARV regimen**

**Key to Acronyms:** ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; COBI = cobicistat; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV/r = darunavir/ritonavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; FLP = fasting lipid profile; FTC = emtricitabine; HDL-C = high-density lipoprotein cholesterol; INSTI = integrase strand transfer inhibitor; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; LPV/r = lopinavir/ritonavir; NHLBI = National Heart, Lung, and Blood Institute; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PUFA = polyunsaturated fatty acid; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglyceride

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**Table 15c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Nausea/Vomiting</b>	<p>All ARVs, but most notably—</p> <p><b>NRTIs:</b></p> <ul style="list-style-type: none"> <li>• ddI and ZDV at a higher rate than others</li> </ul> <p><b>PIs:</b></p> <ul style="list-style-type: none"> <li>• Especially with RTV boosting (e.g., LPV/r, DRV/r)</li> </ul>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Early</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Nausea, emesis—may be associated with anorexia and/or abdominal pain</li> </ul>	Varies with ARV agent; 10% to 30% in some series	Unknown	<p>Instruct patient to take PIs with food.</p> <p>Monitor for weight loss, ARV adherence.</p> <p><b>Do not use ddI, d4T, or NFV (individually or together) as part of an ARV regimen.<sup>a</sup></b></p>	<p>Reassure patient that these adverse effects generally improve over time (usually 6–8 weeks).</p> <p>Supportive care.</p> <p>In extreme or persistent cases, <b>use antiemetics or switch ARV regimen.</b></p>
<b>Diarrhea</b>	<p><b>PIs:</b></p> <ul style="list-style-type: none"> <li>• Particularly NFV, LPV/r, and DRV/r</li> </ul> <p><b>NRTIs:</b></p> <ul style="list-style-type: none"> <li>• ddI and d4T at a higher rate than 3TC or FTC</li> </ul>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Early</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Generally soft, more frequent stools</li> </ul>	Varies with ARV agent; <b>generally &lt;15% (range 5% to 30%)</b>	Unknown	<p>Monitor for weight loss, dehydration.</p> <p><b>Do not use ddI, d4T, or NFV (individually or together) as part of an ARV regimen.<sup>a</sup></b></p>	<p>If prolonged or severe, exclude infectious or noninfectious (e.g., lactose intolerance) causes of diarrhea.</p> <p>Reassure patient that this adverse effect generally improves over time (usually 6–8 weeks). <b>Consider switching ARV regimen in persistent and severe cases.</b></p> <p>Although treatment data in children are lacking, potentially useful modalities include:</p> <ul style="list-style-type: none"> <li>• Dietary modification</li> <li>• Bulk-forming agents (psyllium)</li> <li>• Antimotility agents (loperamide)</li> <li>• Crofelemer is FDA-approved for treatment of ART-associated diarrhea <b>only</b> in adults <b>≥18 years of age; no pediatric data available.</b></li> </ul>

**Table 15c. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Pancreatitis</b>	<p><b>More Common:</b></p> <ul style="list-style-type: none"> <li>• ddl, d4T (especially if administered concurrently)</li> </ul> <p><b>Rare:</b></p> <ul style="list-style-type: none"> <li>• RTV-boosted PIs</li> <li>• Other ARVs</li> </ul>	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>• Anytime, 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 (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis)</li> </ul>	<2% in recent series	<ul style="list-style-type: none"> <li>Use of concomitant medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin)</li> <li>Hypertriglyceridemia</li> <li>Advanced disease</li> <li>Previous episode of pancreatitis</li> <li>Alcohol use</li> </ul>	<b>Do not use</b> ddl or d4T (individually or together) as part of an ARV regimen. <sup>a</sup>	<p>Discontinue offending agent—<b>avoid reintroduction</b>.</p> <p>Manage symptoms of acute episode.</p> <p>If associated with hypertriglyceridemia, consider interventions to lower TG levels.</p>

<sup>a</sup> ddl, d4T, and NFV are **no longer recommended**; these ARVs should not be used (individually or together) as part of an ARV regimen. Co-administration of ddl and d4T is **contraindicated (no exceptions)**.

**Key to Acronyms:** 3TC = lamivudine; ART = antiretroviral therapy; ARV = antiretroviral; d4T = stavudine; ddl = didanosine; DRV/r = darunavir/ritonavir; FDA = Food and Drug Administration; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

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**Table 15d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects** (Last updated May 22, 2018; last reviewed May 22, 2018) (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><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Variable, weeks to months</li> </ul> <p><u>Presentation</u></p> <p><i>Most Commonly:</i></p> <ul style="list-style-type: none"> <li>• Asymptomatic or mild fatigue</li> <li>• Pallor</li> <li>• Tachypnea</li> </ul> <p><i>Rarely:</i></p> <ul style="list-style-type: none"> <li>• Congestive heart failure</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> <li>• Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir.</li> </ul> <p><u>Children with HIV Taking ARVs:</u></p> <ul style="list-style-type: none"> <li>• 2–3 times more common with ZDV-containing regimens</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> <li>• Premature birth</li> <li>• <i>In utero</i> exposure to <b>ZDV-containing regimens</b></li> <li>• Advanced maternal HIV</li> <li>• Neonatal blood loss</li> <li>• Combination ARV prophylaxis, particularly with ZDV plus 3TC</li> </ul> <p><u>Children with HIV Taking ARVs:</u></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>• Malnutrition</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> <li>• Obtain CBC at birth.</li> <li>• Consider repeat CBC at 4 weeks for neonates who are at higher risk (e.g., those born prematurely or known to have low birth Hgb) and if ZDV is continued beyond 4 weeks.</li> </ul> <p><u>Children with HIV Taking ARVs:</u></p> <ul style="list-style-type: none"> <li>• Avoid ZDV in children with severe anemia when alternative agents are available.</li> <li>• Obtain CBC as part of routine care (see <b>Clinical and Laboratory Monitoring</b>)</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> <li>• Anemia rarely requires intervention unless Hgb is &lt;7.0 g/dL or it is associated with symptoms.</li> <li>• <b>ZDV administration can be limited to 4 weeks in low-risk neonates (see <a href="#">Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV</a>).</b></li> </ul> <p><u>Children with HIV Taking ARVs:</u></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 thought to be associated with ARVs (<b>typically macrocytic anemia</b>), switch to a regimen that does not contain ZDV.</li> </ul>
<b>Macrocytosis</b>	ZDV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Within days to weeks of starting therapy</li> <li>• MCV often &gt;100 fL</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Asymptomatic</li> <li>• Sometimes associated with anemia</li> </ul>	>90% to 95%, all ages	None	<p><b>None required—detected if CBC obtained</b> as part of routine care (see <a href="#">Clinical and Laboratory Monitoring section</a>).</p>	None required

**Table 15d. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neutropenia <sup>a</sup>	ZDV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Variable</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Asymptomatic</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> <li>• Rare</li> </ul> <p><u>Children with HIV Taking ARVs:</u></p> <ul style="list-style-type: none"> <li>• 2% to 4% of children on ARVs</li> <li>• Highest rates with ZDV-containing regimens</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <ul style="list-style-type: none"> <li>• <i>In utero</i> exposure to ARVs</li> <li>• Combination ARV prophylaxis, particularly with ZDV plus 3TC</li> </ul> <p><u>Children with HIV Taking ARVs:</u></p> <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>	<p><u>Children with HIV Taking ARVs:</u></p> <ul style="list-style-type: none"> <li>• Obtain CBC as part of routine care.</li> </ul>	<p><u>Newborns Exposed to HIV:</u></p> <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 <u>Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV</u>).</li> </ul> <p><u>Children with HIV Taking ARVs:</u></p> <ul style="list-style-type: none"> <li>• Discontinue non-ARV marrow-toxic drugs, if feasible.</li> <li>• Treat coexisting OIs and malignancies.</li> <li>• For persistent severe neutropenia thought to be associated with ARVs, change to a regimen that does not contain ZDV.</li> </ul>

<sup>a</sup> HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

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

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**Table 15e. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events**  
 (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Hepatitis</b>	<p>Most ARVs have been associated with hepatitis, but there is a strong association with NVP, EFV, and TPV.</p> <p>NVP, EFV, ABC, RAL, and MVC have been associated with hepatitis in context of HSRs.</p> <p>NRTIs have been associated with lactic acidosis and hepatic steatosis, especially ZDV, d4T, and ddI (co-administering d4T and ddI poses the highest risk).</p> <p>d4T or ddI are no longer recommended for use in an ARV regimen.</p>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• An acute toxic hepatitis most commonly occurs within the first few months of therapy (but can occur later).</li> <li>• Steatosis presents after months to years of therapy.</li> <li>• Patients with HBV coinfection may develop flare of hepatitis with the initiation or withdrawal of 3TC, FTC, TDF, or TAF. Flare may also occur with the emergence of resistance to 3TC or FTC (especially if receiving only 1 anti-HBV agent). Note that HBV has a high genetic barrier for resistance to TDF and TAF.</li> <li>• Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-coinfection.</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Asymptomatic elevation of AST and ALT</li> <li>• Symptomatic hepatitis with nausea, fatigue, and jaundice</li> <li>• Hepatitis may present in 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 tridentate</i>], germander [<i>Teucrium chamaedrys</i>])</p> <p>Alcohol use</p> <p>Pregnancy</p> <p><b>Obesity</b></p> <p><u>For NVP-Associated Hepatic Events in Adults:</u></p> <ul style="list-style-type: none"> <li>• Female with pre-NVP CD4 count &gt;250 cells/mm<sup>3</sup></li> <li>• Male with pre-NVP CD4 count &gt;400 cells/mm<sup>3</sup></li> <li>• Population-specific HLA types<sup>a</sup></li> <li>• Higher drug concentrations for PIs, particularly TPV</li> </ul>	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>• Avoid concomitant use of hepatotoxic medications.</li> <li>• Do not use d4T or ddI (individually or together); co-administration is contraindicated (no exceptions).</li> <li>• In patients with elevated hepatic enzymes (&gt;5 to 10 times ULN) or chronic liver disease, most clinicians would avoid NVP.</li> </ul> <p><u>Monitoring</u></p> <p><u>For ARVs Other Than NVP:</u></p> <ul style="list-style-type: none"> <li>• Obtain AST and ALT at baseline and thereafter at least every 3–4 months,<sup>b</sup> or more frequently in at-risk patients (e.g., those with HBV or HCV coinfection or elevated baseline AST and ALT).</li> </ul> <p><u>For NVP:</u></p> <ul style="list-style-type: none"> <li>• Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months.</li> </ul>	<p>Evaluate for other infectious and non-infectious causes and monitor closely.</p> <p><u>Asymptomatic:</u></p> <ul style="list-style-type: none"> <li>• Potentially offending ARVs should be discontinued if ALT or AST is &gt;5 times ULN.</li> </ul> <p><u>Symptomatic:</u></p> <ul style="list-style-type: none"> <li>• Discontinue all ARVs and other potentially hepatotoxic drugs.</li> <li>• If a patient experiences hepatitis attributed to NVP, it should be permanently discontinued.</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 May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Indirect Hyperbilirubinemia</b>	ATV (with either RTV or COBI), IDV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• First months of therapy</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• May be asymptomatic or associated with jaundice</li> <li>• 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 receiving ATV had at least 1 total bilirubin level >5 times ULN and 1.4% experienced jaundice.	N/A	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>• IDV is not FDA-approved or recommended for use in the pediatric population.</li> </ul> <p><u>Monitoring:</u></p> <ul style="list-style-type: none"> <li>• No ongoing monitoring needed.</li> </ul> <p>After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; levels may improve over time.</p>	<p>Isolated indirect hyperbilirubinemia is not indication for cessation of a potentially offending ARV.</p> <p>Psychological impact of jaundice should be evaluated, and alternative agents considered.</p>
<b>Non-Cirrhotic Portal Hypertension</b>	d4T, ddl <b>d4T or ddl are no longer recommended for use in an ARV regimen.</b>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Generally after years of therapy</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• GI bleeding, esophageal varices, hypersplenism</li> <li>• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (due to hypersplenism)</li> </ul> <p><u>Liver Biopsy</u></p> <p><i>Variety of Findings, Most Commonly:</i></p> <ul style="list-style-type: none"> <li>• Nodular regenerative hyperplasia</li> <li>• Hepatoportal sclerosis</li> </ul>	Rare	Prolonged exposure to ARV therapy, especially ddl and the combination of d4T and ddl.	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>• Do not use d4T, or ddl (individually or together); co-administration is contraindicated (no exceptions).</li> </ul> <p><u>Monitoring:</u></p> <ul style="list-style-type: none"> <li>• No specific monitoring</li> </ul>	<p>Discontinue potentially offending agents.</p> <p>Manage complications of GI bleeding and esophageal varices.</p>

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

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

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ALP = alkaline phosphatase; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; COBI = cobicistat; d4T = stavudine; ddl = didanosine; EBV = Epstein-Barr virus; EFV = efavirenz; **FDA = Food and Drug Administration**; FTC = emtricitabine; GI = gastrointestinal; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HLA = human leukocyte antigen; **HSR = hypersensitivity reaction**; IDV = indinavir; IRIS = immune reconstitution inflammatory syndrome; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RTV = ritonavir; **TAF = tenofovir alafenamide**; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; ULN = upper limit of normal; ZDV = zidovudine

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**Table 15f. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated May 22, 2018; last reviewed May 22, 2018)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Insulin Resistance, Asymptomatic Hyperglycemia, DM<sup>a</sup></b>	<p><b>NRTIs:</b></p> <ul style="list-style-type: none"> <li>• ZDV</li> <li>• d4T</li> <li>• ddI</li> </ul> <p><b>d4T or ddI are no longer recommended for use in an ARV regimen.</b></p> <p><b>PIs:</b></p> <ul style="list-style-type: none"> <li>• LPV/r</li> <li>• Rarely other PIs</li> </ul>	<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 (possibly 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%</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>• Lipodystrophy</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> <li>• <b>Do not use d4T or ddI (individually or together); co-administration is contraindicated (no exceptions).</b></li> <li>• <b>Avoid ZDV when possible.</b></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> </ul> <p><i>Obtain RPG Levels at:</i></p> <ul style="list-style-type: none"> <li>• Initiation of ARV therapy</li> <li>• 3–6 months after therapy initiation</li> <li>• Once a year thereafter</li> </ul> <p>For RPG <math>\geq 140</math> mg/dL:</p> <ul style="list-style-type: none"> <li>• Obtain FPG performed after 8-hour fast and consider referral to endocrinologist.</li> </ul>	<p>Counsel on lifestyle modification (e.g., a diet low in saturated fat, cholesterol, trans fat, and refined sugars; increased physical activity; cessation of smoking); recommend consultation with dietician.</p> <p>Change NRTI backbone (e.g., from ZDV, d4T, or ddI to TAF, TDF, or ABC).</p> <p><b>For Either RPG <math>\geq 200</math> mg/dL plus Symptoms of DM or FPG <math>\geq 126</math> mg/dL:</b></p> <ul style="list-style-type: none"> <li>• Patient meets diagnostic criteria for DM; consult endocrinologist.</li> </ul> <p><b>FPG 100–125 mg/dL:</b></p> <ul style="list-style-type: none"> <li>• Impaired FPG is suggestive of insulin resistance; consult endocrinologist.</li> </ul> <p><b>FPG &lt;100 mg/dL</b></p> <p><i>Normal FPG, but Does Not Exclude Insulin Resistance:</i></p> <ul style="list-style-type: none"> <li>• 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 is often defined as elevated insulin levels for the level of glucose observed; *impaired FPG* as an FPG of 100–125 mg/dL; *impaired glucose tolerance* as an elevated 2-hour PG of 140–199 mg/dL in a 75 g-OGTT (or if <43 kg, 1.75 g/kg of glucose up to a maximum of 75 g); and *diabetes mellitus* as either an FPG  $\geq 126$  mg/dL, a random PG  $\geq 200$  mg/dL in a patient with hyperglycemia symptoms, an HgbA1c of  $\geq 6.5\%$ , or a 2-hour PG after OGTT  $\geq 200$  mg/dL. However, the Panel does not recommend routine determinations of insulin levels, HgbA1c, or glucose tolerance without consultation with an endocrinologist. These guidelines are instead based on the readily available RPG and FPG levels.

**Key to Acronyms:** ABC = abacavir; ARV = antiretroviral; BMI = body mass index; d4T = stavudine; ddI = didanosine; dL = deciliter; DM = diabetes mellitus; FPG = fasting plasma glucose; HgbA1c = glycosylated hemoglobin; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; OGTT = oral glucose tolerance test; PG = plasma glucose; PI = protease inhibitor; RPG = random plasma glucose; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine



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**Table 15g. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis**  
(Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Lactic Acidosis</b>	<p><u>NRTIs:</u></p> <ul style="list-style-type: none"> <li>d4T and ddI have the highest risk when co-administered, followed by ZDV.</li> <li>d4T or ddI are not recommended in an ARV regimen.</li> <li>3TC, FTC, ABC, TAF, and TDF are less likely to induce mitochondrial dysfunction of clinical significance.</li> </ul>	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>1–20 months after starting therapy (median onset was 4 months in 1 case series)</li> </ul> <p><u>Presentation</u></p> <p><i>Usually 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, pancreatic, respiratory failure).</p>	<p><b>The following information is based on studies that included d4T and ddI.</b></p> <p><u>Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L)</u></p> <p><i>Adults:</i></p> <ul style="list-style-type: none"> <li>15% to 35% of adults receiving NRTI therapy for &gt;6 months</li> </ul> <p><i>Children:</i></p> <ul style="list-style-type: none"> <li>29% to 32%</li> </ul> <p><u>Symptomatic Severe Hyperlactatemia (&gt;5.0 mmol/L)</u></p> <p><i>Adults:</i></p> <ul style="list-style-type: none"> <li>0.2% to 5.7%</li> </ul> <p><u>Symptomatic Lactic Acidosis/Hepatic Steatosis:</u></p> <ul style="list-style-type: none"> <li>Rare in all age groups (1.3–11 episodes per 1,000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%)</li> </ul>	<p><u>Adults:</u></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>Prolonged NRTI use (particularly d4T and ddI)</li> <li>Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline)</li> <li>Co-administration 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><u>Preterm Infants or Any Neonates before Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days has Been Attained:</u></p> <ul style="list-style-type: none"> <li>Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution). A diminished ability to metabolize propylene glycol may lead to accumulation and potential adverse events.</li> </ul>	<p><u>Prevention:</u></p> <ul style="list-style-type: none"> <li>Do not use d4T or ddI (individually or together) in an ARV regimen; co-administration is contraindicated (no exceptions).</li> <li>Due to the presence of propylene glycol as a diluent, LPV/r oral solution should not be used in preterm neonates or any neonate before a postmenstrual age of 42 weeks and a postnatal age of ≥14 days has been attained.</li> <li>Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.</li> </ul> <p><u>Monitoring</u></p> <p><i>Asymptomatic:</i></p> <ul style="list-style-type: none"> <li>Measurement of serum lactate is not recommended.</li> </ul> <p><i>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 and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases.</li> </ul>	<p><u>Lactate 2.1–5.0 mmol/L (Confirmed with Second Test):</u></p> <ul style="list-style-type: none"> <li>Replace ddI and d4T with other ARVs.</li> <li>As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.</li> </ul> <p><u>Lactate &gt;5.0 mmol/L (Confirmed with Second Test)<sup>b</sup> or &gt;10.0 mmol/L (Any 1 Test):</u></p> <ul style="list-style-type: none"> <li>Discontinue all ARVs.</li> <li>Provide supportive therapy (IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues).</li> </ul> <p><u>Anecdotal (Unproven) Supportive Therapies:</u></p> <ul style="list-style-type: none"> <li>Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C)</li> </ul> <p>Following resolution of clinical and laboratory abnormalities, resume therapy, either with a NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to induce mitochondrial dysfunction (ABC, TAF, or TDF preferred; possibly FTC or 3TC), and lactate should be monitored monthly for at least 3 months.</p>

<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 the results of the confirmatory test.

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

(Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; BMI = body mass index; CD4 = CD4 T lymphocyte; d4T = stavudine; ddl = didanosine; FTC = emtricitabine; HCV = hepatitis C virus; IV = intravenous; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; RBV = ribavirin; **TAF = tenofovir alafenamide**; TDF = tenofovir disoproxil fumarate; THAM = tris (hydroxymethyl) aminomethane; **ZDV = zidovudine**

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**Table 15h. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated May 22, 2018; last reviewed May 22, 2018) (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.	<u>Onset:</u> <ul style="list-style-type: none"> <li>Trunk and limb fat initially increase; peripheral fat wasting may not appear for 12–24 months after ART initiation.</li> </ul>	Varies greatly depending upon measure and comparator group.  Frequency may be up to 15% with current regimens.	Genetic predisposition  Puberty  HIV-associated inflammation  Older age  Longer duration of ART  Body habitus	See below.	See below.  Physicians should perform a regimen review and consider changing the regimen when lipodystrophy occurs.  Improvement following regimen change is variable. Improvement may occur after several months or years, or it may not occur at all.
<b>Central Lipohypertrophy or Lipo-accumulation</b>	Can occur in the absence of ART, but most often associated with PIs and EFV.	<u>Presentation:</u> <ul style="list-style-type: none"> <li>Central fat accumulation with increased abdominal girth, which may include dorsocervical fat pad (buffalo hump) and/or gynecomastia in males or breast hypertrophy in females, particularly with EFV.</li> </ul>	Up to 15% with current regimens	Obesity before initiation of therapy  Sedentary lifestyle	<u>Prevention:</u> <ul style="list-style-type: none"> <li>Calorically appropriate low-fat diet and exercise</li> </ul> <u>Monitoring:</u> <ul style="list-style-type: none"> <li>BMI measurement</li> <li>Body 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).  Recommend smoking cessation (if applicable) to decrease future CVD risk.  Consider switching patient from PIs and EFV to an INSTI.  <u>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:</u> <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—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)**

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Facial/Peripheral Lipoatrophy</b>	Most associated with thymidine analogue NRTIs (d4T > ZDV)	<p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>• Thinning of subcutaneous fat in face, buttocks, and extremities, measured as a decrease in trunk/limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting.</li> </ul>	<ul style="list-style-type: none"> <li>• Up to 15% with currently used regimens</li> </ul>	Underweight before ART	<p><b>Prevention:</b></p> <ul style="list-style-type: none"> <li>• Do not use ddI or d4T (individually or together); they are no longer recommended as part of an ARV regimen. <b>Co-administration of ddI and d4T is contraindicated (no exceptions).</b></li> </ul> <p><b>Monitoring:</b></p> <ul style="list-style-type: none"> <li>• Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy.</li> </ul>	<p>Replace ZDV with other NRTIs if possible. d4T should never be used.</p> <p>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:</p> <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>

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; BMI = body mass index; CVD = cardiovascular disease; d4T = stavudine; DXA = dual energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; ZDV = zidovudine

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See the archived version of [Supplement III](#), February 23, 2009 [Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection](#) (<https://www.aidsinfo.nih.gov>) for a more complete discussion and reference list.

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**Table 15i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects**  
 (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Urolithiasis/ Nephrolithiasis</b>	ATV, IDV  DRV causes crystalluria, but it is not associated with nephrolithiasis.	<u>Onset:</u> <ul style="list-style-type: none"> <li>Weeks to months after starting therapy</li> </ul> <u>Clinical Findings:</u> <ul style="list-style-type: none"> <li>Crystalluria</li> <li>Hematuria</li> <li>Pyuria</li> <li>Flank pain</li> <li>Sometimes increased creatinine</li> </ul>	ATV-related nephrolithiasis occurs in <10% of patients.  IDV-related <b>nephrolithiasis occurs more often</b> in children (29%) than adults (12.4%).	In adults, elevated urine pH (>5.7)  Unknown in children	<u>Prevention:</u> <ul style="list-style-type: none"> <li>Maintain adequate hydration.</li> <li>IDV is not FDA-approved for use in children and should be avoided.</li> </ul> <u>Monitoring:</u> <ul style="list-style-type: none"> <li>Obtain urinalysis at least every 6–12 months.</li> </ul>	Provide adequate hydration and pain control; consider using alternative ARV. If patient is on IDV, discontinue.
<b>Renal Dysfunction</b>	TDF	<u>Onset:</u> <ul style="list-style-type: none"> <li>Variable; in adults, weeks to months after initiation of therapy</li> <li>Hypophosphatemia appears at a median of 18 months.</li> <li>Glucosuria may occur after a year of therapy.</li> <li>Abnormal urine protein/osmolality ratio may be an early indicator.</li> </ul> <u>Presentation</u> <i>More Common:</i> <ul style="list-style-type: none"> <li>Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness</li> </ul> <i>Less Common:</i> <ul style="list-style-type: none"> <li>Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria</li> </ul>	<u>Adults:</u> <ul style="list-style-type: none"> <li>Approximately 2% with increased serum creatinine</li> <li>Approximately 0.5% with severe renal complications</li> </ul> <u>Children:</u> <ul style="list-style-type: none"> <li>Approximately 4% with hypophosphatemia or proximal tubulopathy; frequency increases with prolonged TDF therapy, advanced HIV infection, or concomitant use of ddl.</li> </ul>	<u>Risk May Increase in Children with the Following Characteristics:</u> <ul style="list-style-type: none"> <li>Aged &gt;6 years</li> <li>Black race, Hispanic/Latino ethnicity</li> <li>Advanced HIV infection</li> <li>Hypertension</li> <li>Diabetes</li> <li>Concurrent use of ddl or PIs (especially LPV/r), and preexisting renal dysfunction</li> <li>Risk increases with longer duration of TDF treatment.</li> </ul>	Monitor urine protein, glucose or urinalysis, and serum creatinine at 3- to 6-month intervals. For patients taking TDF, some panelists add serum phosphate to the list of routine labs to monitor.  <b>Measure serum phosphate if the patient experiences</b> persistent proteinuria or glucosuria, or has symptoms of bone pain, muscle pain, or weakness.  Because toxicity risk increases with duration of TDF treatment, do not decrease the frequency of monitoring over time.	If TDF is the likely cause, consider using alternative ARV. TAF has significantly less toxicity than TDF.  <b>ddl is no longer recommended and should be discontinued.</b>

**Table 15i. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects**  
 (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 2)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Elevation in Serum Creatinine</b>	DTG, COBI, RPV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• Within a month of starting treatment</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in eGFR.</li> </ul>	<p>Common</p> <p>Need to distinguish between true change in eGFR and other causes. True change might be associated with other medical conditions, continuing rise of serum creatinine with time, and albuminuria.</p>	N/A	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 patient about the benign nature of the laboratory abnormality.</p>

**Key to Acronyms:** ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; ddl = didanosine; DRV = darunavir; DTG = dolutegravir; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; IDV = indinavir; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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**Table 15j. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis** (Last updated May 22, 2018; last reviewed May 22, 2018)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>Osteopenia and Osteoporosis</b>	Any ART regimen  <u>Specific Agents of Concern:</u> • TDF • PIs, especially LPV/r	<u>Onset:</u> • Any age; decrease in BMD usually seen soon after initiation of ART.  <u>Presentation:</u> • Usually asymptomatic • Rarely presents as osteoporosis, a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma).	<u>BMD z Score Less Than -2.0:</u> • <10% in U.S. cohorts • Approximately 20% to 30% in international cohorts	Longer duration and greater severity of HIV disease  <b>Vitamin D insufficiency/deficiency</b>  Delayed growth or pubertal delay  Low BMI  Lipodystrophy  Non-black race  Smoking  Prolonged systemic corticosteroid use  Medroxyprogesterone use  Lack of weight-bearing exercise	<u>Prevention:</u> • Ensure sufficient calcium intake and vitamin D sufficiency. • Encourage weight-bearing exercise. • Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone).  • <b>Use TAF instead of TDF whenever possible.</b>  <u>Monitoring:</u> • Assess nutritional intake (calcium, vitamin D, and total calories). • <b>Strongly</b> consider measuring serum 25-OH-vitamin D levels, <b>particularly in those patients taking ARVs of concern.</b> <sup>a</sup> • Obtain a DXA. <sup>b</sup>	Same options as for prevention.  Consider changing the ARV regimen (e.g., <b>switching from TDF to TAF, and/or from LPV/r to EFV or an INSTI whenever possible</b> ).  <b>Treat with vitamin D3 to raise serum 25-OH-vitamin D concentrations to &gt;30 ng/mL.</b>  The role of bisphosphonates <b>in managing osteopenia and osteoporosis in children with HIV</b> has not been established.

<sup>a</sup> Some experts periodically measure 25-OH-vitamin D. This is especially important in youth with HIV infection who live in urban areas; the prevalence of vitamin D insufficiency is high in that population.

<sup>b</sup> Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts obtain a DXA at baseline and every 6 to 12 months for prepubertal children and for children in early puberty who are initiating treatment with TDF. Obtaining a DXA could also be considered for adolescent women on TDF and medroxyprogesterone and for children with indications not uniquely related to HIV infection (such as cerebral palsy).

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; BMD = bone mineral density; BMI = body mass index; DXA = dual-energy x-ray absorptiometry; EFV = efavirenz; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TAF= tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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### Osteopenia and Osteoporosis

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**Table 15k. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity** (Last updated May 22, 2018; last reviewed May 22, 2018)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency <sup>a</sup>	Risk Factors	Prevention/Monitoring	Management
<b>ARV Toxic Neuropathy<sup>b</sup></b>	d4T, ddl d4T or ddl are <b>no longer recommended</b> for use in an ARV regimen. PIs rarely, primarily IDV	<b>Onset:</b> • Weeks to months <b>Presentation:</b> • Decreased sensation • Aching, burning, painful numbness • Hyperalgesia • Allodynia • Decreased or absent ankle reflexes <b>Distribution:</b> • Bilateral soles of feet, ascending to legs and fingertips	<b>Children:</b> • Around 1% overall • 10% to 25% in children taking d4T <b>Adults:</b> • Up to 50% in adults taking d4T	<ul style="list-style-type: none"> <li>• Pre-existing neuropathy</li> <li>• Elevated triglyceride levels</li> <li>• Poor nutrition</li> <li>• More advanced HIV disease</li> <li>• Concomitant use of other neurotoxic agents (e.g., INH)</li> <li>• Some mitochondrial DNA haplogroups may have increased risk.</li> </ul>	<p>Do not use d4T, ddl, or IDV. Co-administration of ddl and d4T is <b>contraindicated (no exceptions)</b>.</p> <p>Monitor for symptoms and signs of peripheral neuropathy.</p>	<p>Investigate potential causes, including non-ARV medications and nutritional deficiencies.</p> <p>Discontinue offending agent.</p> <p>Topical capsaicin 8% may be helpful.</p> <p>Consider referral to a neurologist.</p> <p>Data are insufficient to allow the Panel to recommend use of any of the following modalities: tricyclic antidepressants, gabapentin, pregabalin, mexiletine, lamotrigine, and acupuncture or other complementary approaches.</p>

<sup>a</sup> Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

<sup>b</sup> HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

**Key to Acronyms:** ARV = antiretroviral; d4T = stavudine; ddl = didanosine; IDV = indinavir; INH = isoniazid; PI = protease inhibitor; the Panel = The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV

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**Table 15I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 1 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Rash	Any ARV can cause rash	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>First few days to weeks after starting <b>new ARV(s)</b></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 SJS/TEN/EM Major and HSR sections below).</p>	<p><u>Common (&gt;10% Adults and/or Children):</u></p> <ul style="list-style-type: none"> <li>NVP</li> <li>EFV</li> <li>ETR</li> <li>FPV</li> <li>FTC</li> </ul> <p><u>Less Common (5% to 10%):</u></p> <ul style="list-style-type: none"> <li>ABC</li> <li>DRV</li> <li>TPV</li> <li>TDF</li> </ul> <p><u>Unusual (2% to 4%):</u></p> <ul style="list-style-type: none"> <li>LPV/r</li> <li>RAL</li> <li>MVC</li> <li>RPV</li> </ul>	<ul style="list-style-type: none"> <li>Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV)</li> <li>Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP</li> </ul>	<p><u>When Starting NVP or Restarting After Interruptions &gt;14 Days:</u></p> <ul style="list-style-type: none"> <li>Utilize once-daily lead-in dosing (<a href="#">see NVP section</a>).<sup>a</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><u>Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:</u></p> <ul style="list-style-type: none"> <li>Most rashes will resolve without intervention; ARVs can be continued while monitoring.<sup>a</sup></li> <li>Antihistamines may provide some relief.</li> </ul> <p><u>Severe Rash (e.g., Blisters, Bullae, Ulcers, Skin Necrosis) and/or Rash Accompanied by Systemic Symptoms (e.g., Fever, Arthralgia, Edema) and/or Rash Accompanied by Mucous Membrane Involvement (e.g., conjunctivitis):</u></p> <ul style="list-style-type: none"> <li>Manage as SJS/TEN/EM major (see below)</li> </ul> <p><u>Rash in Patients Receiving NVP:</u></p> <ul style="list-style-type: none"> <li>Given elevated risk of HSR, measure hepatic transaminases.</li> <li>If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP below).</li> </ul>
	T-20	<p><b>Onset:</b></p> <ul style="list-style-type: none"> <li>First few days to weeks after starting <b>new ARV(s)</b></li> </ul> <p><b>Presentation:</b></p> <ul style="list-style-type: none"> <li>Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, and ecchymosis</li> <li>Often multiple reactions at the same time</li> </ul>	<p><u>Children and Adults:</u></p> <ul style="list-style-type: none"> <li>&gt;90%</li> </ul>	Unknown	<ul style="list-style-type: none"> <li>Routinely assess patient for local reactions.</li> <li>Rotate injection sites.</li> <li>Massage area after injection.</li> </ul>	<ul style="list-style-type: none"> <li>Continue the agent as tolerated by the patient.</li> <li>Ensure patient is injecting as per instructions.</li> <li>Rotate injection sites.</li> </ul>

**Table 15I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 2 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<b>SJS/TEN/EM Major</b>	Many ARVs, especially NNRTIs (see Estimated Frequency column)	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• First few days to weeks <b>after starting new ARV(s)</b></li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>• Initial rash may be mild, but 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><u>Infrequent:</u></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><u>Case Reports:</u></p> <ul style="list-style-type: none"> <li>• FPV</li> <li>• ABC</li> <li>• DRV</li> <li>• ZDV</li> <li>• ddI</li> <li>• IDV</li> <li>• LPV/r</li> <li>• ATV</li> <li>• RAL</li> </ul>	<p><u>Adults:</u></p> <ul style="list-style-type: none"> <li>• Female gender</li> <li>• Race/ethnicity (black, Asian, Hispanic)</li> </ul>	<p><u>When Starting NVP or Restarting After Interruptions &gt;14 Days:</u></p> <ul style="list-style-type: none"> <li>• Utilize once-daily lead-in dosing (see NVP section).<sup>a</sup></li> <li>• Counsel families to report symptoms as soon as they appear.</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX).</li> <li>• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.</li> <li>• Corticosteroids and/or IVIG are sometimes used, but use of each is controversial.</li> <li>• Do not reintroduce the offending medication.</li> <li>• In case of SJS/TEN/EM major occurring with 1 NNRTI, many experts would avoid use of other NNRTIs.</li> </ul>
<b>DRESS</b>	EFV, ETR, NVP, RAL, RPV, DRV	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>• 1–8 weeks <b>after starting new ARV(s)</b></li> </ul> <p><u>Presentation:</u></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 liver and/or renal)</li> </ul>	Rare	Unknown	<ul style="list-style-type: none"> <li>• Obtain CBC, AST, ALT, and creatinine from a patient presenting with suggestive symptoms.</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue all ARVs and other possible causative agents (e.g., TMP-SMX).</li> <li>• Role for steroids unclear; suggest consultation with specialist.</li> <li>• Provide supportive care for end-organ disease.</li> <li>• Do not reintroduce the offending medication.</li> </ul>

**Table 15I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 3 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
<p><b>HSR</b></p> <p>With or without skin involvement and excluding SJS/TEN</p>	ABC	<p><u>Onset</u></p> <p><i>With First Use:</i></p> <ul style="list-style-type: none"> <li>• Within first 6 weeks</li> </ul> <p><i>With Reintroduction:</i></p> <ul style="list-style-type: none"> <li>• Within hours</li> </ul> <p><u>Presentation:</u></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>• Symptoms worsen to include hypotension and vascular collapse with continuation of ABC. With rechallenge, symptoms can mimic anaphylaxis.</li> </ul>	2.3% to 9% (varies by ethnicity).	<ul style="list-style-type: none"> <li>• HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); combination of HLA-DR7 plus HLA-DQ3 also confers risk.</li> <li>• HSR risk is higher in those of white race compared to those of black or East Asian race.</li> </ul>	<ul style="list-style-type: none"> <li>• Screen for HLA-B*5701. <b>ABC should not be prescribed if HLA-B*5701 is present.</b> The medical record should clearly indicate that ABC is <b>contraindicated</b>.</li> <li>• When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions.</li> </ul>	<ul style="list-style-type: none"> <li>• Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness).</li> <li>• Treat symptoms as necessary.</li> <li>• Most symptoms resolve within 48 hours after discontinuation of ABC.</li> <li>• Do not rechallenge with ABC even if the patient is HLA-B*5701-negative.</li> </ul>

**Table 15I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 4 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR  With or without skin involvement and excluding SJS/TEN	NVP	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>Most frequent in the first few weeks of therapy, but can occur through 18 weeks</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, and jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy</li> </ul>	4% (2.5% to 11%)	<p><u>Adults:</u></p> <ul style="list-style-type: none"> <li>Treatment-naïve with 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 compared with males).</li> </ul> <p><u>Children:</u></p> <ul style="list-style-type: none"> <li>NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults and uncommon in infants.</li> <li>High CD4 percentage is associated with increased risk of NVP toxicity. In the PREDICT study, the risk of NVP toxicity (rash, hepatotoxicity, hypersensitivity) was 2.65 times greater in children who had CD4 percentages ≥15% than in children who had CD4 percentages &lt;15%.</li> </ul>	<p><u>When Starting NVP or Restarting After Interruptions &gt;14 Days:</u></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></li> <li>Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.</li> <li>Obtain AST and ALT in patients with rash. Obtain AST and ALT at baseline, before dose escalation, 2 weeks post-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 post-exposure prophylaxis outside of the neonatal period.</li> </ul>	<ul style="list-style-type: none"> <li>Discontinue ARVs.</li> <li>Consider other causes for hepatitis and discontinue all hepatotoxic medications.</li> <li>Provide supportive care as indicated and monitor the patient closely.</li> <li>Do not re-introduce NVP. The safety of other NNRTIs is unknown following symptomatic hepatitis due to NVP, and many experts would avoid the NNRTI drug class when restarting treatment.</li> </ul>
	T-20, ETR	<p><u>Onset:</u></p> <ul style="list-style-type: none"> <li>Any time during therapy</li> </ul> <p><u>Presentation:</u></p> <ul style="list-style-type: none"> <li>Symptoms may include rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.</li> </ul>	Rare	Unknown	<ul style="list-style-type: none"> <li>Evaluate for hypersensitivity if the patient is symptomatic.</li> </ul>	<p>Discontinue ARVs.</p> <p>Rechallenge with T-20 or ETR is not recommended.</p>

**Table 15I. Antiretroviral-Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions** (Last updated May 22, 2018; last reviewed May 22, 2018) (page 5 of 5)

Adverse Effects	Associated ARVs	Onset/Clinical Manifestations	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
HSR  With or without skin involvement and excluding SJS/TEN	MVC	Rash preceding hepatotoxicity	Rare	Unknown	<ul style="list-style-type: none"> <li>Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</li> </ul>	<ul style="list-style-type: none"> <li>Discontinue all ARVs.</li> <li>Rechallenge with MVC is not recommended.</li> </ul>
	DTG	Rash with hepatic dysfunction	Rare	Unknown	<ul style="list-style-type: none"> <li>Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity.</li> </ul>	<ul style="list-style-type: none"> <li>Discontinue all ARVs.</li> <li>Rechallenge with DTG is contraindicated</li> </ul>

<sup>a</sup> The prescribing information for NVP states that patients experiencing 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 risk of NVP resistance because of sub-therapeutic drug levels. Management of children who have persistent mild or moderate rash after the lead-in period should be individualized and an expert in HIV care should be consulted. **NVP should be stopped and not restarted** if the rash is severe or is worsening or progressing.

**Key to Acronyms:** ABC = abacavir; ALT = alanine transaminase; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CBC = complete blood count; CD4 = CD4 T lymphocyte; CYP = cytochrome P; ddl = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ETR = etravirine; FPV = fosamprenavir; FTC = emtricitabine; HLA = human leukocyte antigen; HSR = hypersensitivity reaction; IDV = indinavir; 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; T-20 = enfuvirtide TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

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# Management of Children Receiving Antiretroviral Therapy (Last updated May 22, 2018; last reviewed May 22, 2018)

In the United States, the majority of children living with HIV are receiving antiretroviral therapy (ART), making treatment-experienced children the norm. Changes to the antiretroviral (ARV) regimen and other aspects of the management of treatment-experienced children can be organized into the following categories:

1. Modifying ARV regimens in children who are currently receiving effective ART in order to simplify the regimen or to improve the adverse event profile
2. Recognizing and managing ARV drug toxicity or intolerance (see [Management of Medication Toxicity or Intolerance](#))
3. Recognizing and managing treatment failure
4. Increasing the treatment potency or barrier to resistance of an effective, but older or potentially fragile, regimen

## 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, and decreases the risk of drug-associated toxicity (<b>AII</b>).</li><li>• All past regimens and past episodes of ARV therapy failure, tolerability, and all prior drug resistance testing results should be considered in order to avoid choosing new ARV drugs for which archived drug resistance would limit antiviral activity (<b>AIII</b>).</li><li>• Children should be carefully monitored after a change in treatment. Viral load measurement is recommended 2 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>

Initial antiretroviral (ARV) regimens are chosen based on the safety, pharmacokinetic, and efficacy data available regarding formulations suitable for the child's age at start of treatment. New ARV options may become available as children grow and learn to swallow pills, and as new drugs, drug formulations, and data become available. Even in cases where patients have experienced sustained virologic suppression (e.g., 6–12 months) on their current regimen, changing to a new ARV regimen should be considered in order to permit use of pills instead of liquids, reduce pill burden, allow use of once-daily medications, reduce risk of adverse events (AEs), minimize drug interactions, and align a child's regimen with widely used, efficacious adult regimens.<sup>1</sup> Often the changes enhance adherence and improve quality of life.<sup>2</sup>

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. According to the results of the NEVEREST 2 study, young children (i.e., those aged <2 years) with virologic suppression who switch from lopinavir/ritonavir (LPV/r) to nevirapine can maintain virologic suppression as well as those who continue taking LPV/r, provided that there is good adherence and no baseline resistance to nevirapine.<sup>3,4</sup> In the NEVEREST 3 study, children aged ≥3 years with a history of

exposure to nevirapine and with virologic suppression on LPV/r continued to maintain virologic suppression when switched from LPV/r to efavirenz.<sup>5-7</sup> Similarly, in the NEVEREST 2 study, children who switched to a nevirapine regimen showed better immune and growth responses than those who stayed on a LPV/r regimen.<sup>3</sup> By extrapolation, replacing LPV/r with an equally potent protease inhibitor (PI) (e.g., darunavir, atazanavir) or an integrase strand transfer inhibitor (INSTI) (e.g., elvitegravir, raltegravir, dolutegravir) would likely be effective, but these substitutions have not been directly studied in children. Several studies in small cohorts of children have demonstrated sustained virologic suppression and reassuring safety outcomes when drugs that have greater long-term toxicity risk are replaced with drugs that are thought to have less toxicity risk (e.g., replacing stavudine with tenofovir disoproxil fumarate, tenofovir alafenamide, zidovudine, or abacavir; replacing PIs with non-nucleoside reverse transcriptase inhibitors), including improved lipid profiles.<sup>8-12</sup> Small studies have shown that children who achieve virologic suppression on certain twice-daily regimens (i.e., abacavir, nevirapine) maintain virologic suppression if changed from twice-daily to once-daily regimens (see the [Abacavir](#) and [Nevirapine](#) drug sections). However, these studies show mixed results when switching LPV/r dosing from twice daily to once daily; therefore, once-daily LPV/r is not recommended in children aged <12 years or weighing <30 kg.<sup>13-15,16</sup>

Dual and monotherapy PI (darunavir/ritonavir, LPV/r, atazanavir/ritonavir)<sup>17,18</sup> and **monotherapy** INSTI (dolutegravir) strategies<sup>19,20</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 are not currently recommended as management strategies. Limited studies on these strategies have been done in children, and these strategies cannot be endorsed at this time.<sup>18,21-24</sup> **The fixed-dose combination (FDC) of dolutegravir/rilpivirine (Juluca), a nucleoside-sparing dual-therapy regimen, was recently approved by the Food and Drug Administration (FDA) as a complete regimen to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 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- or four-drug regimens were randomized to either switch to dolutegravir/rilpivirine or to stay on their original regimens. Results from these trials showed similar virologic suppression rates in both groups (noninferiority) through 48 weeks.<sup>25</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 adult formulations for use in adolescents, and this product may be appropriate for selected adolescents. However, because this treatment simplification strategy has not been evaluated in adolescents, who may have difficulties adhering to therapy, the Panel does not recommend use of the FDC Juluca for adolescents and children until more data are available.**

Table 16 displays examples of changes in ARV regimen components that are made for reasons of simplification, convenience, and safety profile in children who have sustained virologic suppression on their current regimen. When considering such a change, a clinician should first ensure that a recent viral load test indicates that the child does not have virologic treatment failure **and that the child has a reliable history of good adherence**. It is also critical to consider antiretroviral therapy (ART) history, tolerability, and all prior drug resistance testing results in order to avoid choosing new ARV drugs for which archived drug resistance would reemerge and limit activity.<sup>26-30</sup> The evidence supporting 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 that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimen (page 1 of 2)**

**Note:** This list is not exhaustive and does not necessarily contain all potential treatment options. Instead, it shows examples of what kinds of changes can be made. The comments provided in the table are relevant only to the potential ARV change are listed and do not include all relevant information. Please refer to the individual drug sections in [Appendix A: Pediatric Antiretroviral Drug Information](#) for further information.

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Switch	Comment
<b>NRTIs</b>			
<b>ABC or 3TC Twice Daily</b>	Aged ≥1 year	ABC once daily	See <a href="#">Abacavir<sup>a</sup></a> and <a href="#">Lamivudine</a> sections in <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> for full discussion of <b>once-daily dosing</b> .
	Aged ≥3 years	<b>3TC once daily</b>	
<b>ZDV, ddl, or d4T<sup>b</sup></b>	Aged ≥3 months	ABC	<b>Less long-term mitochondrial toxicity.</b> Children <b>aged ≥1 year</b> can take ABC once daily (see <a href="#">Abacavir<sup>a</sup></a> in <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> ).
	Aged ≥2 years	<b>TDF</b>	TDF is a reasonable, once-daily option for HLA-B*5701–positive children who are unable to take ABC. TDF is available in <b>low-strength combination tablets with FTC</b> for use in children weighing <b>≥17 kg</b> . TAF is preferred for children weighing <b>≥25 kg</b> .
	Weighing ≥25 kg	TAF <sup>c</sup>	<b>Less long-term mitochondrial toxicity. Once-daily dosing. Co-formulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone and renal toxicity. See <a href="#">TAF</a> in <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> for full discussion.</b>
<b>NNRTIs</b>			
<b>EFV</b>	N/A	<b>RAL<sup>d</sup></b>	None
	Aged ≥3 months Weighing ≥5 kg	ATV/r	None
	Aged ≥3 years Weighing ≥10 kg	DRV/r	DRV/r may be administered once daily in children aged ≥12 years who do not have DRV resistance mutations.
	Weighing ≥25 kg	<b>EVG as Genvoya</b>	<b>EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya). Genvoya is a complete ARV regimen.</b>
	Weighing ≥30 kg	DTG	Smaller pill, higher barrier to resistance given concern for adherence challenges developing in adolescents.
	Aged ≥12 years Weighing ≥35 kg	RPV	None
<b>PIs</b>			
<b>LPV/r Twice Daily</b>	N/A	<b>RAL<sup>d</sup></b>	None
	Aged ≥3 years Weighing ≥10 kg	EFV	Once-daily dosing. Better palatability. Lower incidence of adverse lipid effects. See <a href="#">Efavirenz</a> in <a href="#">Appendix A: Pediatric Antiretroviral Drug Information</a> regarding concerns about dosing for children aged <3 years.
	Aged ≥3 months Weighing ≥5 kg	ATV/r	Once-daily dosing.
	Aged ≥3 years Weighing ≥10 kg	<b>DRV/r</b>	<b>DRV/r is administered twice daily to patients aged &lt;12 years, but may be administered once daily only in children aged ≥12 years who do not have DRV resistance mutations.</b>
	Weighing ≥25 kg	<b>EVG as Genvoya</b>	<b>EVG is available as a component of the FDC EVG/COBI/FTC/TAF (Genvoya). Genvoya is a complete ARV regimen.</b>

**Table 16. Examples of Changes in Antiretroviral Regimen Components that Are Made for Reasons of Simplification, Convenience, and Safety Profile in Children Who Have Sustained Virologic Suppression on Their Current Regimen (page 2 of 2)**

Current ARV Drug(s)	Age, Weight, and SMR Requirements	Potential ARV Switch	Comment
LPV/r  Twice Daily, continued	Weighing ≥30 kg	DTG	None
	Aged ≥12 years Weighing ≥35 kg	RPV <b>BIC as Biktarvy</b>	None <b>Once-daily dosing. BIC is available as a component of the FDC BIC/FTC/TAF (Biktarvy). Biktarvy is a complete ARV regimen; pediatric use is investigational.</b>
<b>Other</b>			
<b>Any Multi-Pill and/or Twice-Daily Regimen</b>	Weighing ≥25 kg	EVG/COBI/FTC/TAF (Genvoya)	Once-daily dosing. Single pill. Alignment with adult regimens.
	<b>Weighing ≥30 kg</b>	FTC/TAF <sup>a</sup> (Descovy) plus DTG	Once-daily dosing. May be more desirable because of small pill sizes, even though it increases pill burden to 2 pills instead of 1.
	<b>Weighing ≥35 kg SMR 4 or 5</b>	EVG/COBI/FTC/TDF (Stribild)	Once-daily dosing. Single pill. Alignment with adult regimens.
	<b>Aged ≥12 years Weighing ≥35 kg</b>	FTC/RPV/TAF (Odefsey)	Once-daily dosing. Single pill. Alignment with adult regimens.
	<b>Aged ≥12 years Weighing ≥35 kg</b>	<b>BIC/FTC/TAF<sup>a</sup> (Biktarvy)</b>	<b>Once-daily dosing. Single pill. Pediatric use is investigational.</b>
	<b>Aged ≥12 years Weighing ≥35 kg SMR 4 or 5</b>	FTC/RPV/TDF (Complera)	Once-daily dosing. Single pill. Alignment with adult regimens.
	<b>Weighing ≥40 kg</b>	ABC/DTG/3TC (Triumeq)	Once-daily dosing. Single pill. Alignment with adult regimens. <b>Large pill size may be a deterrent.</b>
	<b>Weighing ≥40 kg SMR 4 or 5</b>	EFV/FTC/TDF (Atripla)	Once-daily dosing. Single pill. Alignment with adult regimens.

<sup>a</sup> For infants and young children being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In clinically stable patients with undetectable viral loads who have had stable CD4 T lymphocyte cell counts for more than 6 months (24 weeks) on twice-daily ABC, the dose can be changed from twice daily to once daily.

<sup>b</sup> d4T and ddI should be replaced with a safer drug **as soon as possible** because of concerns about long-term adverse events (see [Stavudine](#) and [Didanosine](#) 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 HD once daily is only recommended for virologically suppressed children weighing ≥50 kg.

<sup>e</sup> Biktarvy has not been FDA-approved for use in patients aged <18 years but is being studied in children and adolescents aged ≥12 years to 18 years and weighing ≥35 kg.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; **BIC = bictegravir**; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; **FDC = fixed-dose combination**; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; SMR = sexual maturity rating (previously Tanner stages); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV= tenofovir; ZDV = zidovudine

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## Recognizing and Managing Antiretroviral Treatment Failure (Last updated May 22, 2018; last reviewed May 22, 2018)

### Panel's Recommendations

- The causes of antiretroviral (ARV) treatment failure—which include poor adherence, drug resistance, poor absorption of medications, inadequate dosing, and drug-drug interactions—should be assessed and addressed (**AII**).
- Perform ARV drug-resistance testing when virologic failure occurs, while the patient is still taking the failing regimen, and before changing to a new regimen (**AI\***).
- ARV regimens should be chosen based on treatment history and drug-resistance testing, including both past and current resistance test results (**AI\***).
- The new regimen should include at least two, but preferably three, fully active ARV medications, with assessment of anticipated ARV activity based on past treatment history and resistance test results (**AII\***).
- The goal of therapy following treatment failure is to achieve and maintain virologic suppression, as measured by a plasma viral load below the limits of detection using the most sensitive assay (**AI\***).
- When complete virologic suppression cannot be achieved, the goals of therapy are to preserve or restore immunologic function (as measured by CD4 T lymphocyte values), prevent clinical disease progression, and prevent development of additional drug resistance that could further limit future ARV options (**AII**).
- Children who require evaluation and management of treatment failure should be managed by or in collaboration with a pediatric HIV specialist (**AI\***).

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

**Rating of Evidence:** I = One or more randomized trials in children<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

### Categories of Treatment Failure

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

### Virologic Failure

Virologic failure occurs as an incomplete initial response to therapy or as a viral rebound after virologic suppression is achieved. *Virologic suppression* is defined as having plasma viral load below the lower level of detection (LLD), as measured by highly sensitive assays with lower limits of quantitation (LLQ) of 20 to 75 copies/mL. *Virologic failure* is defined as a repeated 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 treatment failure is made. Infants with high plasma viral loads at initiation of therapy occasionally take longer than 6 months to achieve virologic suppression. Because of this, some experts continue the treatment regimen for infants receiving lopinavir/ritonavir (LPV/r)-based therapy if viral load is declining but is still  $\geq 200$  copies/mL at 6 months and monitor closely for continued decline to virologic suppression.<sup>1</sup> However, ongoing non-suppression—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 between the LLD and <200 copies/mL in patients on antiretroviral therapy (ART). Adults with HIV who have detectable viral loads and a quantified result <200 copies/mL after 6 months of ART generally achieve virologic suppression without regimen change.<sup>4-6</sup> However, some studies in adults have found that multiple viral load measurements of 50 to <200 copies/mL may be associated with an increased risk of later virologic failure.<sup>7,8</sup> “Blips”—defined as isolated episodes of plasma viral load detectable at low levels (i.e., <500 copies/mL) followed by a return to viral suppression—are common and not generally reflective of virologic failure.<sup>9-11</sup> However, repeated or persistent plasma viral load detection  $\geq 200$  copies/mL (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.<sup>6,11-13</sup>

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

Poor immunologic response despite virologic suppression is uncommon in children.<sup>14</sup> Patients with baseline severe immunosuppression often take more than 1 year to achieve immune recovery (i.e., CD4 T lymphocyte [CD4] cell count >500 cells/mm<sup>3</sup>), even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur.

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

Patients who have very low baseline CD4 values before initiating ART are at higher risk of an impaired CD4 response to ART and, based on adult studies, may be at higher risk of death and AIDS-defining illnesses, despite virologic suppression.<sup>15-17</sup> In a study of 933 children aged  $\geq 5$  years who received ART that resulted in virologic suppression, 348 (37%) had CD4 cell counts <500 cells/mm<sup>3</sup> at ART initiation, including 92 (9.9%) with CD4 cell counts <200 cells/mm<sup>3</sup>. After 1 year of virologic suppression, only 7 (1% of the cohort) failed to reach a CD4 cell count  $\geq 200$  cells/mm<sup>3</sup> and 86% had CD4 cell counts >500 cells/mm<sup>3</sup>. AIDS-defining events were uncommon overall (1%) but occurred in children who did and did not achieve improved CD4 cell counts.<sup>14</sup>

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

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

### **Poor Clinical Response Despite Adequate Virologic and Immunologic Responses**

Clinicians must carefully evaluate patients who experience clinical disease progression despite favorable immunologic and virologic responses to ART. Not all cases represent ART failure. IRIS is one of the most important reasons that new or recurrent opportunistic conditions occur, even in cases where virologic suppression and immunologic restoration/preservation are achieved within the first months of ART. IRIS does not represent ART failure and does not generally require discontinuation of ART.<sup>18,19</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>20</sup> Such

cases do not represent ART failure and, in these instances, children would not benefit from a change in ARV regimen. Before a definitive conclusion of ART clinical failure is reached, a child should also be evaluated to rule out (and, if indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary TB, malnutrition, and malignancy. Occasionally, however, children will develop new HIV-related opportunistic conditions (e.g., *Pneumocystis jirovecii* pneumonia or esophageal candidiasis occurring more than 6 months after achieving markedly improved CD4 values and virologic suppression) not explained by IRIS, pre-existing organ damage, or another reason.<sup>14</sup> Although such cases are rare, they may represent ART clinical failure and suggest that improvement in CD4 values may not necessarily normalize immunologic function. In children who have signs of new or progressive abnormal neurodevelopment, some experts change the ARV regimen, aiming to include agents that are known to achieve higher concentrations in the central nervous system; however, the data supporting this strategy are mixed.<sup>21,22</sup>

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

<b>Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression</b>
<p><u>Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response:</u></p> <ul style="list-style-type: none"> <li>• Lab error (in CD4 or viral load result)</li> <li>• Misinterpretation of normal, age-related CD4 decline (i.e., the immunologic response is not actually poor)</li> <li>• Low pretreatment CD4 cell count or percentage</li> <li>• Adverse effects of using ZDV or the combination of TDF and ddl</li> <li>• Use of systemic corticosteroids or chemotherapeutic agents</li> <li>• Conditions that can cause low CD4 values, such as HCV, acute viral infections, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis</li> </ul> <p><u>Poor Immunologic and Clinical Responses Despite Virologic Suppression:</u></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 (HIV-1 non-M groups, non-B subtypes; HIV-2)</li> <li>• Persistent immunodeficiency soon after initiation of 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>• 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), lungs (e.g., bronchiectasis)</li> <li>• New clinical event due to non-HIV illness or condition</li> <li>• New, otherwise unexplained HIV-related clinical event (treatment failure)</li> </ul>

**Key to Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; ddl = didanosine; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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

The approach to management and subsequent treatment of virologic treatment failure will differ depending on the etiology of the problem. While the causes of virologic treatment failure may be multifactorial, nonadherence plays a role in most cases. Assessment of a child with suspected virologic treatment failure should include evaluation of therapy adherence and medication intolerance, confirmation that prescribed dosing is correct (and understood by the child and/or caregiver) for all medications in the regimen, consideration of pharmacokinetic (PK) explanations of low drug levels or elevated and potentially toxic

levels, and evaluation of suspected drug resistance (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Guidelines](#)). The main barrier to long-term maintenance of sustained virologic suppression in adults and children is incomplete adherence to medication regimens, with subsequent emergence of viral mutations conferring partial or complete resistance to one or more of the components of the ART regimen. Please see guidance on assessment of adherence and strategies to improve adherence.

### **Virologic Treatment Failure with No Viral Drug Resistance Identified**

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

Virologic failure of boosted protease inhibitor (PI)-based regimens (in the absence of prior treatment with full-dose ritonavir) is frequently associated with no detectable major PI resistance mutations. Virologic suppression may be achieved by continuing the PI-based regimen and taking adherence improvement measures.<sup>23,24</sup>

In some cases, if a new more convenient regimen is available that is anticipated to address the main barrier to adherence, it may be reasonable to change to this new regimen (e.g., a single fixed-dose tablet once daily) with close adherence and viral load monitoring. In most cases, however, when there is evidence of poor adherence to the current regimen and an assessment that good adherence to a new regimen is unlikely, emphasis and effort should be placed on improving adherence before initiating a new regimen (see [Adherence to Antiretroviral Therapy](#)).

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

After deciding that a change in therapy is needed, a clinician should attempt to identify at least two, but preferably three, fully active ARV agents from at least two different classes **on the basis of all past and recent drug resistance test results**, prior ARV exposure, acceptability to the patient, and likelihood of adherence.<sup>25-29</sup> This often requires using agents from one or more drug classes that are new to the patient. Substitution or addition of a single drug to a failing regimen is not recommended because it is unlikely to lead to durable virologic suppression and will likely result in additional drug resistance. A drug may be new to the patient but have diminished antiviral potency due to the presence of drug-resistance mutations that confer cross-resistance within a drug class.

The process of switching a patient to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with the patient and the patient's caregivers. This discussion should be age- and development-appropriate for the patient. Clinicians must recognize that conflicting requirements of some medications with respect to food and concomitant medication restrictions may complicate administration of a regimen. Timing of medication administration is particularly important to ensure adequate ARV drug exposures throughout the day. Palatability, size and number of pills, and dosing frequency all need to be considered when choosing a new regimen.<sup>30</sup>

### ***Therapeutic Options After Virologic Treatment Failure with Goal of Complete Virologic Suppression***

Determination of a new regimen with the best chance for complete virologic suppression in children who have already experienced treatment failure should be made by or in collaboration with a pediatric HIV



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

If a child experiences failure of initial therapy with an NNRTI-based regimen, a change to a PI-based regimen is generally effective. Studies of adults have found no evidence that a boosted PI regimen that includes raltegravir produces better outcomes than a boosted PI regimen that contains two NRTIs. Therefore, most children who experience treatment failure on an initial NNRTI-based regimen should be changed to a regimen of a boosted PI plus two NRTIs.<sup>31,32</sup> Limited data support the use of two NRTIs plus an INSTI following failure of an NNRTI-based regimen.<sup>33,34</sup> **Evidence from a trial in adults supports superior outcomes for dolutegravir compared to LPV/r when used in a second-line regimen that includes at least one active NRTI, following failure of an initial NNRTI-based regimen.**<sup>35</sup> There is concern about this approach (especially when using INSTIs with a lower barrier to resistance, such as raltegravir), because children who experience treatment failure on NNRTI-based regimens often have substantial NRTI resistance.<sup>36</sup> Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. The NNRTIs etravirine and rilpivirine can retain activity against nevirapine- or efavirenz-resistant virus in the absence of certain key NNRTI mutations (see below), but etravirine has generally been tested only in regimens that also contain a boosted PI.

If a child experiences initial therapy failure with a PI-based regimen, there is often limited resistance detected,<sup>36,37</sup> in which case an alternative PI that is better tolerated and potent can be used. For example, LPV/r-based regimens have been shown to have durable ARV activity in some PI-experienced children.<sup>38-40</sup> Darunavir/ritonavir-based therapy has also been used.<sup>41,42</sup> Based on more limited data, a change to an INSTI-based regimen can be effective.<sup>33,43</sup>

The availability of newer drugs in existing classes and newer classes of drugs increases the likelihood of finding three active drugs, even for children with extensive drug resistance (see [Table 18](#)). As discussed, INSTI-based regimens are increasingly used for children who have experienced treatment failure on NNRTI- or PI-based regimens.<sup>33,43</sup> Raltegravir is the INSTI that has been studied and used most in children, but dolutegravir (see the [Dolutegravir](#) section for latest age/weight indications) is increasingly appealing for its once-daily administration, small pill size, and higher barrier to development of drug resistance, including activity in patients who have experienced treatment failure on raltegravir-based therapy. Maraviroc, a CCR5 antagonist, provides a new drug class, but many treatment-experienced children already harbor CXCR4-tropic virus that precludes its use.<sup>44</sup> Regimens including an INSTI and potent, boosted PI plus or minus etravirine have been effective in small studies of extensively ARV-experienced patients with multiclass drug resistance.<sup>45-48</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 more detailed information on drug formulation, pediatric and adult dosing, and toxicity, as well as discussion of available pediatric data for the approved ARV drugs.

Previously prescribed drugs that were discontinued because of poor tolerance or poor adherence may sometimes be reintroduced if ARV resistance did not develop and if prior difficulties with tolerance and adherence can be overcome (e.g., by switching from a liquid to a pill formulation or to a new formulation [e.g., ritonavir tablet **or a fixed-dose combination tablet**]). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication, despite the presence of lamivudine resistance mutations. Continuation of lamivudine can also maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations, conferring resistance to zidovudine, stavudine, and tenofovir disoproxil fumarate.<sup>49-51</sup> The use of new drugs that have been evaluated in adults but have not been fully evaluated in children may be justified, and ideally would be done in the framework of a clinical trial. Expanded access programs or clinical trials may be available (see [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). New drugs should be used in combination with at least one, and ideally two, additional active agents.

Enfuvirtide has been Food and Drug Administration-approved for use in treatment-experienced children aged  $\geq 6$  years, but it must be administered by subcutaneous injection twice daily.<sup>52,53</sup> PK studies of certain dual-boosted PI regimens (LPV/r with saquinavir) suggest that PK targets for both PIs can be achieved or exceeded when used in combination in children.<sup>54-56</sup> Multidrug regimens (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>57</sup> Availability of newer PIs (e.g., darunavir for children aged  $\geq 3$  years) and new classes of ARV drugs (integrase and CCR5 inhibitors) have lessened the need for use of enfuvirtide, dual-PI regimens, and regimens of four or more drugs.

Studies of NRTI-sparing regimens in adults with virologic failure and multidrug resistance have demonstrated no clear benefit of including NRTIs in the new regimen,<sup>58,59</sup> and one of these studies reported higher mortality in adults randomized to a regimen with NRTIs compared to adults randomized to an NRTI-sparing regimen.<sup>59</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 and future use of newer therapeutic agents that may not have been studied or approved in children or may be in clinical development. Information concerning potential clinical trials can be found at the [AIDSinfo Clinical Trial Search](#) and through collaboration with 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>60</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>61</sup>

Use of ARV agents that do not have a pediatric indication (i.e., off-label) may be necessary for children with HIV who have limited ARV options. In this circumstance, consultation with 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 non-suppressive regimen must be made on an individual basis, weighing potential benefits and costs. Specifically, HIV 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 (i.e., nonadherence, non-suppressive suboptimal regimen). Non-suppressive 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>62</sup> However, persistent viremia in the context of ARV 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 continuing non-suppressive 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 complete interruption of therapy is not recommended. One trial (IMPAACT P1094) randomized children harboring the M184V resistance mutation with persistent

nonadherence and virologic failure to continue their non-suppressive, non-NNRTI-based ART regimen or switch to a lamivudine (or emtricitabine) monotherapy holding regimen. Children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 cell count (the primary outcome) over a 28-week period. The median age of the participants was 15 years, the median entry CD4 cell count was 472 cells/mm<sup>3</sup>, and the median number of interventions that had been used to address nonadherence was four. Only patients in the lamivudine/emtricitabine arm experienced the primary outcome.<sup>63</sup> Although this was a small study (N = 33), it is the only study ever to randomize patients to either continue non-suppressive ART or switch to lamivudine/emtricitabine monotherapy, and it is unlikely that it will be repeated.

Complete treatment interruption has also been associated with immunologic declines and poor clinical outcomes, and it is not recommended (see [Considerations About Interruptions in Antiretroviral Therapy](#)).<sup>64,65</sup>

**Table 18. Options for Regimens with at Least Two Fully Active Agents with Goal of Virologic Suppression in Patients with Failed Antiretroviral Therapy and Evidence of Viral Resistance<sup>a</sup>**

Prior Regimen	New Regimen Options <sup>a</sup>
2 NRTIs plus NNRTI	<ul style="list-style-type: none"> <li>• 2 NRTIs plus PI</li> <li>• 2 NRTIs plus INSTI</li> </ul>
2 NRTIs plus PI	<ul style="list-style-type: none"> <li>• 2 NRTIs plus INSTI</li> <li>• 2 NRTIs plus a different RTV-boosted PI</li> <li>• INSTI plus different RTV-boosted PI plus or minus an NNRTI and plus or minus NRTI(s)</li> </ul>
2 NRTIs plus INSTI	<ul style="list-style-type: none"> <li>• 2 NRTIs plus RTV-boosted PI</li> <li>• DTG (if not used in the prior regimen) plus RTV-boosted PI plus or minus 1 or 2 NRTIs</li> </ul>
Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)	<ul style="list-style-type: none"> <li>• INSTI plus 2 NRTIs (if NRTIs are fully active)</li> <li>• INSTI plus 2 NRTIs plus or minus RTV-boosted PI (if NRTIs are not fully active)</li> <li>• INSTI plus or minus RTV-boosted PI plus or minus (ETR or RPV) plus or minus NRTI(s) (if minimal NRTI activity). Consider adding T-20 and/or MVC if additional active drug[s] needed.</li> </ul>

<sup>a</sup> ART regimens should be chosen based on treatment history and drug-resistance testing to optimize ARV drug effectiveness. This is particularly important in selecting 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. **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.

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

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## Considerations About Interruptions in Antiretroviral Therapy (Last updated May 22, 2018, last reviewed May 22, 2018)

### 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<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

### Unplanned Interruptions

Temporary discontinuation of antiretroviral therapy (ART) may be unavoidable in some situations, such as in cases of serious treatment-related toxicity or acute illnesses or planned surgeries that preclude oral intake. Lack of available medication may also require temporary ART discontinuation. **Children from limited-resource settings often experience interruptions due to drugs being out of stock locally or poor access to medication during the immigration process.** Prolonged interruptions of ART can also result from disengagement from care or other social or psychologic 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 (median 12.1 months). Interruption was associated with lower CD4 T lymphocyte cell (CD4) percentages at 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 with 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. **To prevent interruptions in children planning extended travel, such as immigrant children returning to home countries, local drug access or multiple-month drug dispensation should be arranged ahead of time.** Additional guidance on supporting adherence can be found in [Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV](#).

### Structured Treatment Interruptions

Planned periods during which ART is not given, also known as “structured treatment interruptions,” were historically considered as a potential strategy to reduce toxicity, costs, and drug-related failure associated with ART.

Adult trials demonstrated significantly higher morbidity and mortality in participants randomized to undergo structured treatment interruptions than in participants who received 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 Guidelines](#)).

There have been fewer studies in children of long-term structured treatment interruption. In one study, children with controlled viral load (i.e., HIV RNA <400 copies/mL for >12 months) were subjected to increasing durations of treatment interruption. Of 14 children studied, four maintained undetectable viral



loads with interruptions of up to 27 days. It has been hypothesized that enhanced HIV-specific immune responses may play a role in the viral suppression.<sup>7</sup> However, new drug-resistance mutations were detected in three out of 14 children in the structured treatment interruption study. In a European trial (PENTA 11), 109 children with virologic suppression on ART were randomized to receive continuous therapy (CT) or treatment interruption with CD4-guided re-initiation of ART.<sup>8</sup> On average, CD4 values decreased sharply in the first 10 weeks after structured treatment interruption. However, only 34% (19/56) of children in the structured treatment interruption arm reached the required CD4 criteria to restart therapy within 48 weeks. Children in the structured treatment interruption arm spent significantly less time on ART than children in the CT arm. None of the children in the trial experienced serious clinical illnesses or events, and the appearance of new drug-resistance mutations did not differ between the two arms.

In the ARROW trial, every month of treatment interruption among children was associated with 2% lower CD4 percentage (with a range of 1% to 3%,  $P = 0.001$ ) at 3 years of follow-up; having any interruption of treatment was associated with an increased risk of mortality during that time period [hazard ratio: 2.6 (95% CI, 0.7–10.4)].<sup>9</sup> In some populations of children, structured treatment interruption has been more specifically considered. The CHER trial in South Africa was designed to answer whether infants who initiated ART early could safely discontinue therapy at some point and re-initiate treatment based on CD4 cell decline. The study assessed outcomes in infants randomized to receive deferred ART (initiation driven by Centers for Disease Control and Prevention [CDC] stage and CD4 status), immediate ART with interruption after 40 weeks, or immediate ART with interruption after 96 weeks.<sup>10,11</sup> While the two arms that received immediate ART followed by interrupted therapy had better outcomes than the deferred arms, up to 80% of infants had to restart therapy by the end of follow-up. In another trial, 42 children who had initiated ART at age <13 months (and had CD4 percentages >25% with normal growth) were randomized to undergo treatment interruption or to continue ART.<sup>12</sup> Treatment was re-initiated in the treatment interruption arm if children met what were World Health Organization ART eligibility criteria at the time. Of the 21 infants in the treatment interruption arm, 12 met ART restart criteria within 3 months and randomization was stopped by the Data Safety Monitoring Board. No differences in CD4 percentage, virologic control, or morbidity were seen at 18 months. The long-term outcomes of infants in both trials are 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 ART in some infants (see [Antiretroviral Management of Newborns](#)).<sup>13–15</sup> However, that infant eventually experienced viral rebound, and there have been other reports of infants who have experienced immediate rebound of viral load after cessation of ART despite having undetectable HIV DNA and RNA while on ART.<sup>16,17</sup> The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend treatment interruption as a strategy to confirm diagnosis or to assess for remission or cure in infants who revert to negative serology or negative HIV DNA testing.

### Short-Cycle Treatment Strategies

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

A more recent study suggests that shorter cycles off ART may 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/2 days off) or CT.<sup>19,20</sup> At enrollment, participants were virologically suppressed (viral load <50 copies/mL for >12 months) and receiving efavirenz plus two nucleoside reverse transcriptase inhibitors. By 48 weeks, six participants (6%) in the SCT arm and seven participants (7%) in the CT arm had a confirmed

virological failure (viral load >50 copies/mL) [difference -1.2%, 90% CI, -7.3% to 4.9%]. Of the six participants in the SCT arm with failure, five resuppressed. Three of those participants resuppressed on the same regimen and two resuppressed with a regimen switch; two others on SCT resumed daily ART for other reasons. Seven participants (SCT, n = 2; CT, n = 5) had major non-nucleoside reverse transcriptase inhibitor mutations 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 appreciated the option of SCT.<sup>21</sup> A preliminary report about long-term follow-up of children in the BREATHER study (which included 194 of the original 199 children) suggests comparable virological failure rates between the SCT and CT arms (both arms had a failure rate of approximately 16%) after a median 3.6 years. The participants in the SCT arm experienced a greater number of serious adverse events than participants in the CT arm (21 serious adverse events in the SCT arm vs. eight in the CT arm, driven by hospitalizations), but both arms experienced comparable rates of CDC-stage and Grade 3 or 4 adverse events. In summary, the BREATHER trial suggests that SCT with efavirenz-based ART may be safe in some adolescents and may yield increased satisfaction that could lead to better long-term adherence. However, the Panel believes that additional data are needed to decide whether this strategy would be safe in different patient populations, with different ART regimens, outside of the context trial, and over longer periods of time.

## Conclusion

Most studies have shown that treatment interruption in children appears to result in only short periods of time off ART and yields only minimal potential benefits to counterbalance the risks and limited long-term follow-up data. Lower toxicity of current antiretroviral agents decreases the potential benefits of treatment interruptions. It is possible that short-cycle treatment strategies may be safe for some patients, but additional data are needed. At the present time, the Panel does not recommend structured treatment interruption in the clinical care of children with HIV; additional studies of treatment interruption strategies in specific situations may be warranted.

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

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### **Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors**

Abacavir (ABC, Ziagen)

Didanosine (ddI, Videx)

Emtricitabine (FTC, Emtriva)

Lamivudine (3TC/Epivir)

Stavudine (d4T, Zerit)

Tenofovir Disoproxil Fumarate (TDF, Viread)

Zidovudine (ZDV, AZT, Retrovir)

## Abacavir (ABC, Ziagen) (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:** 300 mg (scored)

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

#### Fixed-Dose Combination Tablets:

- [Epzicom] Abacavir 600 mg plus lamivudine 300 mg
- [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

#### Generic Formulations:

- Abacavir sulfate 300 mg tablets
- Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg
- Fixed-dose combination tablets of abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not approved for infants aged <3 months.

#### Pediatric Dose

*Oral Solution (Aged ≥3 Months):*

- 8 mg/kg (maximum 300 mg per dose) twice daily or 16 mg/kg once daily (maximum 600 mg per dose) (see text below).
- In infants and young children being treated with liquid formulations of abacavir, initiation with once-daily abacavir is not generally recommended. In clinically stable patients with undetectable viral load and stable CD4 T lymphocyte (CD4) cell count/percentage for more than 6 months (24 weeks) on liquid formulation of abacavir twice daily, dose can be changed from twice daily to once daily with liquid or tablet formulations (see text below).

#### Weight Band Dosing (Weighing ≥14 kg)

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

### Selected Adverse Events

- Hypersensitivity reactions (HSR) 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 and shortness of breath).

### Special Instructions

- Test patients for the HLA-B\*5701 allele before starting therapy to predict risk of HSR. Patients positive for the HLA-B\*5701 allele should not be given abacavir. Patients with no prior HLA-B\*5701 testing who are tolerating abacavir do not need to be tested.
- Warn patients and parents about risk of serious, potentially fatal HSRs. Occurrence of HSRs requires **immediate and permanent discontinuation** of abacavir. **Do not re-challenge.**
- Abacavir can be given without regard to food. Oral solution does not require refrigeration.
- **When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.**

- In patients who can be treated with pill formulations, therapy can be initiated with once-daily administration.

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

- 300 mg twice daily or 600 mg once daily.

#### **[Trizivir] Abacavir plus Lamivudine plus Zidovudine**

*Adolescent (Weighing  $\geq$ 40 kg) and Adult Dose:*

- One tablet twice daily.

#### **[Epzicom] Abacavir plus Lamivudine**

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

- One tablet once daily.

#### **[Triumeq] Abacavir plus Dolutegravir plus Lamivudine**

*Adolescent (Weighing  $\geq$ 40 kg) and Adult Dose:*

- One tablet once daily.

- For use in patients who are antiretroviral (ARV) treatment-naïve or treatment-experienced (but INSTI-naïve) and not being treated with UGT1A1/CYP3A inducers.

## **Metabolism/Elimination**

- Systemically metabolized by alcohol dehydrogenase and glucuronyltransferase.
- Active metabolite is 82% renally excreted.
- Abacavir requires dosage adjustment in hepatic insufficiency.
- Do not use fixed-dose combinations such as Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents), in patients with impaired hepatic function because the dose of abacavir cannot be adjusted.
- Do not use Trizivir, Epzicom, and Triumeq (or the fixed-dose combination's generic equivalents) in patients with creatinine clearance  $<$ 50 mL/min and patients on dialysis (because of the fixed dose of lamivudine).

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

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P (CYP) 450 enzymes. Therefore, it does not cause **significant** changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors. Abacavir plasma area under the **drug-concentration-by-time curve** (AUC) has been reported to be decreased by 17% and 32% with concurrent use of the PIs atazanavir/ritonavir and lopinavir/ritonavir (LPV/r), respectively.<sup>1</sup> Another study reported decrease in plasma abacavir AUC by 40% with concurrent use of LPV/r; however, the intracellular metabolite carbovir triphosphate concentrations appeared to be increased with LPV/r exposure.<sup>2</sup> Co-administration with darunavir/ritonavir has produced a decrease in abacavir plasma AUC and trough concentrations by 27% and 38%, respectively; the carbovir triphosphate AUC and trough concentrations were also decreased by 12% and 32%, respectively.<sup>3</sup> The mechanism and the clinical significance of these drug interactions with the PIs are unknown. No dose adjustments for abacavir or PIs are currently recommended.
- Through interference with alcohol dehydrogenase and glucuronyltransferase, **alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) has been shown to increase abacavir AUC plasma exposure by 41% in adult men with HIV receiving 600 mg of abacavir daily.**<sup>4</sup>
- **Abacavir oral solution contains sorbitol, which decreased exposure of concurrently administered lamivudine solution in adults.**<sup>5</sup>

### **Major Toxicities**

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, and anorexia.
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) observed in approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir. HSR to abacavir is a multi-organ clinical syndrome usually characterized by rash or signs or symptoms in two or more of the following groups:

- Fever
- Constitutional, including malaise, fatigue, or achiness
- Gastrointestinal, including nausea, vomiting, diarrhea, or abdominal pain
- Respiratory, 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. This reaction generally occurs in the first 6 weeks of therapy, but has also been reported after a single dose. If a HSR is suspected, abacavir **should be stopped immediately and not restarted—hypotension and death may occur upon re-challenge**. The risk of abacavir HSR is associated with the presence of HLA-B\*5701 allele; it is greatly reduced by not using abacavir in those who test positive for the HLA-B\*5701 allele.
- *Rare*: Increased liver enzymes, elevated blood glucose, elevated triglycerides, and possible increased risk of myocardial infarction (in observational studies in adults). Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Pancreatitis can occur.
- *Rare*: Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome
- *Rare*: Several observational cohort studies suggest increased risk of myocardial infarction in adults with recent or current use of abacavir; however, other studies have not substantiated this finding, and there are no data in children.

### **Resistance**

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

### **Pediatric Use**

#### *Approval*

Abacavir is Food and Drug Administration (FDA)-approved for use in children **aged 3 months and older** with HIV infection as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy.

#### *Efficacy*

Abacavir used either twice daily or once daily has demonstrated durable antiviral efficacy in pediatric clinical trials and is of comparable efficacy to other NRTIs in children.<sup>6-10</sup> Abacavir in combination with lamivudine has been compared to tenofovir disoproxil fumarate (TDF) with emtricitabine in several adult studies and meta-analyses with variable results.<sup>11-14</sup>

### **Pharmacokinetics**

#### *Pharmacokinetics in Children*

Pharmacokinetic (PK) studies of abacavir in children aged <12 years have demonstrated that children have more rapid clearance of abacavir than adults. Metabolic clearance of abacavir 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>15</sup>

The PK of abacavir dosed once daily in pediatric subjects (aged 3 months through 12 years) with HIV-1 infection was evaluated in three crossover, open-label PK trials of twice- versus once-daily dosing of abacavir and lamivudine (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).<sup>4,16-19</sup> **PK abacavir modeling based on the data from these three pediatric trials predicted overall equivalent systemic plasma abacavir exposure after once- or twice-daily dosing regimens in infants and children up to age 12 years.**<sup>16-20</sup>

These trials, in combination with PK modeling, demonstrated that once-daily abacavir dosing with either the tablet or liquid formulation provides comparable plasma PK exposures to twice-daily dosing of abacavir at the same total daily dose.<sup>21</sup>

## Dosing

### Dosing and Formulations

The initially recommended abacavir dose for pediatric use was 8 mg/kg/dose twice daily, or 16 mg/kg total daily dose. A 2015 FDA review suggested that a total daily dose of 600 mg of abacavir could be safely used in a 25-kg person (i.e., 24 mg/kg/day, a 50% increase from the previously recommended dose). The weight band dosing table recommends total daily doses as high as 21.5 to 22.5 mg/kg/day when treating with the tablet formulation.<sup>4</sup> There is no difference in the abacavir plasma  $C_{max}$  and AUC for abacavir liquid formulation compared to tablet formulation.<sup>22</sup> Doses of liquid abacavir formulation are similar to those used for weight band dosing with tablet formulations and might be considered in some situations, especially in rapidly growing younger children.

In all three abacavir dosing pediatric trials described above,<sup>16-19</sup> only children who had low viral loads and who were clinically stable on twice-daily formulation of abacavir were eligible to change to once-daily abacavir dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily abacavir (336 children) versus twice-daily abacavir (333 children) in tablet formulation combined with a once- or twice-daily lamivudine-based antiretroviral regimen.<sup>8</sup> To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir liquid formulation. In children who can be treated with pill formulations, initiation of therapy with once-daily dosing of abacavir (at a dose of 16 mg/kg/dose [maximum of 600 mg] once daily) is recommended. However, in infants and young children initiating therapy with liquid formulations of abacavir, twice-daily dosing is recommended, and switching to once-daily dosing after 6 months (24 weeks) should be considered if viral load is undetectable and CD4 cell count/percentage is stable (without decline).

## Toxicity

Abacavir has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,<sup>6,7</sup> and less bone and renal toxicity when compared to TDF.<sup>13,23</sup>

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## 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-naive 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

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>

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## Emtricitabine (FTC, Emtriva) (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

**Capsules:** 200 mg

**Fixed-Dose Combination Tablets:**

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

### Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) for information about the prevention of perinatal transmission.

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

*Oral Solution:*

- 3 mg/kg once daily

#### Pediatric (Aged ≥3 Months to 17 Years) Dose

*Oral Solution:*

- 6 mg/kg (to a maximum dose of 240 mg) once daily; the maximum dose of oral solution is higher than the capsule dose because the oral solution has 20% lower plasma exposure in pediatric pharmacokinetic analysis.

*Capsules (Patients Weighing >33 kg):*

- 200 mg once daily

#### Adolescent (Aged ≥18 Years) and Adult Dose

*Oral Solution for Those Unable to Swallow*

*Capsules:*

- 240 mg (24 mL) once daily

*Capsules:*

- 200 mg once daily

### Selected Adverse Events

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

### Special Instructions

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

### Metabolism/Elimination

- No cytochrome P (CYP) 450 interactions
- Renal excretion of emtricitabine is 86%.

### [Truvada] Emtricitabine plus TDF (FTC/TDF)

*Pediatric Dose:*

#### Truvada Pediatric Dosing Table

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

*Adolescent (Weighing ≥35 kg) and Adult Dose:*

- 1 FTC/TDF 200 mg/300 mg tablet once daily

### [Descovy] Emtricitabine plus TAF

*Pediatric and Adolescent (Weighing ≥25 kg) and Adult Dose:*

- *Body Weight 25 to <35 kg:* 1 tablet once daily in combination with other antiretroviral (ARV) agents, except for protease inhibitors (PIs) that require a CYP3A inhibitor (i.e., emtricitabine/TAF [Descovy] can be used in combination with an integrase strand transfer inhibitor [INSTI] or a non-nucleoside reverse transcriptase inhibitor [NNRTI], but not a boosted PI)
- *Body Weight ≥35 kg:* 1 tablet once daily in combination with an INSTI, NNRTI, or boosted PI

### [Atripla] Efavirenz plus Emtricitabine plus TDF

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

- 1 tablet once daily
- Administer without food.

### [Complera] Emtricitabine plus Rilpivirine plus TDF

*Adolescent (Weighing ≥35 kg) and Adult Dose:*

- 1 tablet once daily in antiretroviral treatment (ART)-naïve patients who have baseline plasma HIV-1 RNA <100,000 copies/mL. This Complera dose 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-1 RNA <50 copies/mL) for at least 6 months with no history of virologic failure or resistance to the individual components of Complera.
- Administer with a meal of at least 500 calories.

Emtricitabine may compete with other compounds that undergo renal elimination.

#### Emtricitabine Dosing in Patients with Renal Impairment:

- Decrease dose in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use the FDC Atripla in patients with creatinine clearance (CrCl) <50 mL/min or in patients who require dialysis.
- Do not use the FDCs Truvada or Biktarvy in patients with CrCl <30 mL/min. Do not use Truvada in patients who require dialysis.
- Use Complera with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring 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 patients with estimated CrCl <30 mL/min.



### **[Odefsey] Emtricitabine plus Rilpivirine plus TAF**

*Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- 1 tablet once daily as initial therapy in ART-naive patients with HIV-1 RNA  $\leq 100,000$  copies per mL. This Odefsey dose can also be used to replace a stable ART regimen in patients who have been virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.
- Administer with a meal of at least 500 calories.

### **[Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF**

*Adolescent (Weighing  $\geq 35$  kg with a Sexual Maturity Rating of 4 or 5) and Adult Dose:*

- 1 tablet once daily **with food** in ART-naive patients. This Stribild dose can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.

### **[Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF**

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

- 1 tablet once daily with food in ART-naive patients. This Genvoya dose can also be used to replace the current ART regimen in patients who have been virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

### **[Biktarvy] Bictegravir plus Emtricitabine plus TAF**

*Pediatric and Adolescent Dose (Aged  $< 18$  Years):*

- Biktarvy has not been Food and Drug Administration-approved for use in patients aged  $< 18$  years.
- *Children aged  $< 12$  years:* No data on appropriate dose of Biktarvy in children aged  $< 12$  years
- *Children and adolescents (aged  $\geq 12$  to 18 years and weighing  $\geq 35$  kg):* 1 tablet once

daily. This is an **investigational dose**.

**Adult Dose (Aged ≥18 Years):**

- 1 tablet once daily in ART-naive patients. This Biktarvy dose can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.
- See the [Bictegravir](#) section for additional information.

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

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* **Do not use** emtricitabine in combination with lamivudine because these agents share similar resistance profiles and lack additive benefit. **Do not use** emtricitabine separately with Combivir, Epzicom, or Trizivir because lamivudine is a component of these fixed-dose combinations. **Do not use** emtricitabine separately when prescribing Truvada, Atripla, Complera, Biktarvy, Stribild, Genvoya, Descovy, or Odefsey because emtricitabine is a component of these fixed-dose combinations. Please see other sections of the [drug appendix](#) for drug interaction information about each individual component when using these fixed-dose combinations.
- *Renal elimination:* Emtricitabine competes with other compounds that undergo renal elimination (possible competition for renal tubular secretion). Drugs that decrease renal function could decrease clearance of emtricitabine.

**Major Toxicities**

- *More common:* Headache, insomnia, diarrhea, nausea, rash, and hyperpigmentation/skin discoloration (possibly more common in children)
- *Less common (more severe):* Neutropenia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Exacerbations of hepatitis have occurred in patients with HIV and hepatitis B virus (HBV) who changed from emtricitabine-containing to non-emtricitabine-containing regimens.

**Resistance**

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

**Pediatric Use**

*Approval*

Emtricitabine is Food and Drug Administration approved for once-daily administration in children, starting at birth. Owing to its once-daily dosing, minimal toxicity, and pediatric pharmacokinetic (PK) data, emtricitabine is used as part of a dual-NRTI backbone in antiretroviral therapy.

**Efficacy and Pharmacokinetics**

*Comparative Clinical Trials*

Studies assessing the efficacy and/or potency of nucleoside/nucleotide analogues have been more concerned

with the dynamic components of the regimen, such as tenofovir or abacavir, than the more static components, such as emtricitabine or lamivudine. Emtricitabine and lamivudine have been considered interchangeable, but there are little data to support this perspective in antiretroviral (ARV)-naive patients. Investigators studying the ATHENA cohort compared the efficacy of tenofovir disoproxil fumarate (TDF) plus emtricitabine or TDF plus lamivudine in combination with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir) in ARV-naive patients.<sup>1</sup> The adjusted hazard ratio for virologic failure of lamivudine-containing regimens compared to emtricitabine-containing regimens within 240 weeks of starting therapy was 1.15 (95% CI; 0.58–2.27). There was also no difference in time to virologic suppression in the first 48 weeks of therapy or time to virologic failure after attaining suppression. Yang et al. in the Swiss cohort found a potential difference in efficacy that disappeared after adjusting for pill burden.<sup>2</sup> Current evidence suggests that emtricitabine and lamivudine have equivalent efficacy and toxicity in ARV-naive patients.

### *Efficacy*

Based on a dose-finding study by Wang et al. (described in the Pharmacokinetics: Liquid Versus Capsule subsection below),<sup>3</sup> emtricitabine 6 mg/kg once daily 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 dosage of 240 mg of the emtricitabine liquid formulation. PK results showed that plasma exposures were similar to those in adults receiving emtricitabine 200 mg once daily. Follow-up data extending to Week 96 indicated that 89% of the ARV-naive children and 76% of the ARV-experienced children maintained plasma HIV RNA <400 copies/mL (75% of ARV-naive children and 67% of ARV-experienced children had HIV RNA <50 copies/mL). Minimal toxicity was observed in this trial. PACTG P1021<sup>5</sup> studied ARV-naive children aged 3 months to 21 years using emtricitabine 6 mg/kg (with a maximum of emtricitabine 200 mg/day of the liquid formulation) in combination with didanosine and efavirenz, all given once daily. Eighty-five percent of children achieved HIV RNA <400 copies/mL, and 72% of children maintained HIV RNA suppression at <50 copies/mL through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm<sup>3</sup> at Week 96.

### *Pharmacokinetics: Liquid Versus Capsule*

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

### *Pharmacokinetics in Infants*

A study in South Africa evaluated the PKs of emtricitabine in 20 infants aged <3 months with perinatal HIV exposure. The participants received a dose of emtricitabine 3 mg/kg once daily for two 4-day courses, separated by an interval of  $\geq 2$  weeks.<sup>6</sup> Emtricitabine exposure (area under the curve [AUC]) in neonates receiving emtricitabine 3 mg/kg once daily was in the range of pediatric patients aged >3 months receiving the recommended dose of emtricitabine 6 mg/kg once daily and adults receiving the once-daily recommended dose of emtricitabine 200 mg (AUC approximately 10 hr\* $\mu\text{g/mL}$ ). Over the first 3 months of life, emtricitabine AUC decreased with increasing age, correlating with an increase in total body clearance of the drug. In a small group of neonates (N = 6) receiving a single dose of emtricitabine 3 mg/kg after a single maternal dose of 600 mg during delivery, the AUC exceeded that seen in adults and older children, but the half-life (9.2 hours) was similar.<sup>7</sup> Extensive safety data are lacking for this age range.

### *Considerations for Use*

Formulations favor liquid emtricitabine over liquid lamivudine, since liquid emtricitabine can be given once daily at ARV initiation but liquid lamivudine needs to be given twice daily at ARV initiation. When pill formulations can be administered, lamivudine and emtricitabine are equivalent.

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

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## Lamivudine (3TC, Epivir) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

#### Pediatric Oral Solution:

- 10 mg/mL [Epivir]
- 5 mg/mL [Epivir HBV<sup>a</sup>]

#### Tablets:

- 150 mg (scored) and 300 mg [Epivir]
- 100 mg [Epivir HBV<sup>a</sup>]

#### Generic Formulations:

Tablets: 100 mg, 150 mg, and 300 mg

#### Fixed-Dose Combination Tablets:

- [Combivir and Generic] Lamivudine 150 mg plus zidovudine 300 mg
- [Epzicom] Abacavir 600 mg plus lamivudine 300 mg
- [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Trizivir] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg
- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

### Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12](#) for information about preventing perinatal transmission.

#### Neonate ( $\geq 32$ Weeks Gestation at Birth) and Infant (Birth to $< 4$ Weeks) Treatment Dose:

- 2 mg/kg twice daily (oral solution)

#### Pediatric Dose

**Note:** In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine **is not recommended**. Patients can be transitioned to once-daily treatment with the oral solution when they have been stable on twice-daily treatment for 36 weeks and are aged  $\geq 3$  years. Please see the note below and refer to the text for more detail.

#### Aged $\geq 4$ Weeks to $< 3$ Months:

- 4 mg/kg twice daily of the oral solution

#### Aged $\geq 3$ Months to $< 3$ Years:

- 5 mg/kg twice daily of the oral solution, up to 150 mg

#### Aged $\geq 3$ Years:

- 5 mg/kg twice daily of the oral solution, up to

### Selected Adverse Events

- Exacerbation of hepatitis has been reported after discontinuation of lamivudine in the setting of chronic hepatitis B virus (HBV) infection.

### Special Instructions

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

### Metabolism/Elimination

- Dose adjustment required in patients with renal insufficiency.
- Fixed-dose combination tablets should not be used in patients who are on dialysis or who have creatinine clearance  $< 50$  mL/min or impaired hepatic function.

150 mg; *or*

- 10 mg/kg once daily of the oral solution, up to 300 mg

**Weighting  $\geq 14$  kg and Able to Swallow Pills:**

- Weight-band dosing (see table below; dose approximate lamivudine 5 mg/kg/day twice daily or 10 mg/kg once daily)

**Weight-Band Dosing (Children Weighing  $\geq 14$  kg)  
Scored 150-mg Tablet**

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

**Note:** The scored tablet is the preferred formulation for pediatric patients weighing  $\geq 14$  kg who can swallow a solid-dosage form.

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports switching children to once-daily dosing of lamivudine (oral solution or tablets) from twice-daily dosing in children aged  $\geq 3$  years, who have been clinically stable for 36 weeks with an undetectable viral load and stable CD4 T lymphocyte count. Clinicians should use a reasonable, once-daily regimen with the once-daily dose of lamivudine indicated above (approximately 10 mg/kg to a maximum of 300 mg once daily).

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

- 150 mg twice daily, *or*
- 300 mg once daily

**[Combivir and Generic] Lamivudine plus Zidovudine**

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

- One tablet twice daily

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

*Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet twice daily

**[Epzicom] Abacavir plus Lamivudine**

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

- One tablet once daily

### **[Triumeq] Abacavir plus Dolutegravir plus Lamivudine**

*Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- One tablet once daily
- For use in patients who are antiretroviral (ARV) treatment-naïve or treatment-experienced (but integrase strand transfer inhibitor-naïve) and who are not being treated with UGT1A1/CYP3A inducers.

### **[Symfi Lo] Efavirenz plus Lamivudine plus TDF**

*Pediatric (Weighing  $\geq 35$  kg) and Adult Dose:*

- One tablet once daily on an empty stomach

**Note:** The new fixed-dose combination (Symfi Lo) with a lower dose of efavirenz has not yet been discussed by the Panel. The Panel will address its use in children in a later update.

<sup>a</sup> Eпивir HBV oral solution and tablets contain a lower amount of lamivudine than Eпивir oral solution and tablets. The amount of lamivudine in the Eпивir HBV solution and tablet was based on dosing for treatment of HBV infection (in people without HIV coinfection). If Eпивir HBV is used in patients with HIV, the higher dose indicated for HIV therapy should be used as part of an appropriate combination regimen. The Eпивir HBV tablet is appropriate for use in children who require a dose of lamivudine 100 mg for treatment of HIV.

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

- Drugs that decrease renal function could decrease clearance of lamivudine.
- Do not use lamivudine in combination with emtricitabine, because these drugs have similar resistance profiles and using them together offers no additional benefit.<sup>1</sup> Do not use lamivudine separately when also prescribing Truvada, Atripla, Complera, or Stribild, because emtricitabine is a component of these formulations.
- Do not use lamivudine separately when prescribing Combivir, Epzicom, Symfi Lo, or Trizivir, because lamivudine is already a component of these combinations.

### **Major Toxicities**

- *More common:* Headache, nausea.
- *Less common (more severe):* Peripheral neuropathy, lipodystrophy/lipoatrophy.
- *Rare:* Increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported.

### **Resistance**

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

### **Pediatric Use**

#### *Approval*

Lamivudine is Food and Drug Administration (FDA)-approved for the treatment of children aged  $\geq 3$  months. It is a common component of most nucleoside backbone regimens.

### *Considerations for Use*

The efficacy and toxicity of lamivudine are equivalent to the efficacy and toxicity of emtricitabine. Formulations favor liquid emtricitabine over liquid lamivudine, since liquid emtricitabine can be given once daily at antiretroviral (ARV) initiation, but liquid lamivudine needs to be given twice daily at ARV initiation. In cases where pill formulations can be administered, lamivudine and emtricitabine are equivalent.

### *Comparative Clinical Trials*

Studies assessing the efficacy and/or potency of nucleoside/nucleotide analogues have been more concerned with the dynamic components of the regimen (e.g., tenofovir disoproxil fumarate (TDF) or abacavir), instead of more static components like emtricitabine or lamivudine. Emtricitabine and lamivudine have been considered interchangeable, but little data exist to support this idea in ARV-naïve patients. Investigators compared treatment-naïve patients in the ATHENA cohort who started TDF/emtricitabine or TDF/lamivudine in combination with a boosted protease inhibitor (darunavir, atazanavir, or lopinavir).<sup>2</sup> The adjusted hazard ratio for virologic failure of lamivudine compared to virologic failure of emtricitabine within 240 weeks of starting therapy was 1.15 (95% CI, 0.58–2.27). There was also no difference between the two groups in time to virologic suppression in the first 48 weeks of therapy or time to virologic failure after attaining suppression. Yang et al. in the Swiss cohort found a potential difference in efficacy that disappeared after adjusting for pill burden. Current evidence suggests that emtricitabine and lamivudine are equivalent even in ARV-naïve patients.<sup>3</sup>

### *Efficacy*

Lamivudine has been studied in children with HIV both alone and in combination with other ARV drugs. Extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response. It is commonly used in children with HIV as a component of a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone.<sup>4-12</sup> In one study, the NRTI background components of lamivudine plus abacavir were superior to zidovudine plus lamivudine or zidovudine plus abacavir in long-term virologic efficacy.<sup>13</sup>

### *Pharmacokinetics in Infants*

Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.<sup>9</sup> A population pharmacokinetic (PK) analysis of infants receiving lamivudine affirms that adjusting the dose of lamivudine from 2 mg/kg to 4 mg/kg every 12 hours at age 4 weeks for infants with normal maturation of renal function provides optimal lamivudine exposure.<sup>14</sup> For infants in early life, the higher World Health Organization weight-band dosing (which is up to five times the FDA dose) results in greater plasma concentrations than the 2 mg/kg dosing.<sup>15</sup> In HPTN 040, lamivudine was given for prophylaxis of perinatal transmission during the first 2 weeks of life along with nelfinavir and 6 weeks of zidovudine according to a weight-band dosing scheme. All infants weighing >2,000 g received lamivudine 6 mg twice daily and infants weighing ≤2,000 g received lamivudine 4 mg twice daily for 2 weeks. These doses resulted in lamivudine exposure similar to that seen in infants who received the standard 2 mg/kg/dose twice-daily dosing schedule for neonates.<sup>16</sup>

### *Pharmacokinetics of Liquid versus Tablet Preparations*

The PK of lamivudine has been studied after either single or repeat doses in 210 pediatric subjects. Pediatric subjects receiving lamivudine oral solution according to the recommended dosage regimen achieved plasma concentrations of lamivudine that were approximately 25% lower than those of adults with HIV receiving oral solution. Pediatric subjects receiving lamivudine oral tablets achieved plasma concentrations comparable to or slightly higher than those observed in adults receiving tablets. In pediatric subjects, the relative bioavailability of lamivudine oral solution is approximately 40% lower than the relative bioavailability of tablets containing lamivudine, despite no difference in adults. The mechanisms for the diminished relative bioavailability of lamivudine solution are unknown,<sup>17</sup> but results from a study in adults that compared the PK of lamivudine solution administered either alone or with increasing concentrations of sorbitol indicates



that sorbitol decreases the total exposure of lamivudine 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, and this may explain the PK discrepancy between the oral solution and tablet formulations. Modeling of PK data in pediatric patients suggests that increasing the lamivudine oral solution dose to 5 mg/kg/dose twice daily or 10 mg/kg/dose once daily (with a maximum of 300 mg administered daily) in children aged  $\geq 3$  months would provide exposures similar to that of adult patients receiving tablet formulations. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend once-daily dosing of lamivudine until a child is aged  $\geq 3$  years. This new dosing, however, is now reflected in the lamivudine package insert, even though there are no clinical data from patients receiving lamivudine who are also receiving sorbitol-containing medications.

#### *Dosing Considerations—Once-Daily versus Twice-Daily Administration*

The standard adult dose for lamivudine is 300 mg once daily, but few data are available regarding once-daily administration of lamivudine in children. Population PK data indicate that once-daily dosing of lamivudine 8 mg/kg leads to area under the curve (AUC)<sub>0-24</sub> values that are similar to those seen in patients taking 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 year to 18 years.<sup>19</sup> Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in children with HIV aged 2 years to 13 years in the PENTA 13 trial,<sup>4</sup> and in children aged 3 months to 36 months in the PENTA 15 trial.<sup>20</sup> Both the PENTA 13 and PENTA 15 trials used a crossover design with lamivudine doses of 8 mg/kg/once daily or 4 mg/kg/twice daily. AUC<sub>0-24</sub> and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children aged 3 years to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent AUC<sub>0-24</sub> and good clinical outcome (disease stage and CD4 T lymphocyte [CD4] cell count) after a switch to once-daily lamivudine, with median follow-up of 1.15 years.<sup>21</sup> This same group conducted a randomized, noninferiority trial that investigated once-daily versus twice-daily doses of lamivudine in more than 600 pediatric patients who initiated therapy with twice-daily lamivudine and had been receiving therapy for at least 36 weeks. Median follow-up time during the study was 114 weeks. The viral load suppression and adverse event profiles for once-daily lamivudine were noninferior to those of twice-daily lamivudine.<sup>22</sup>

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

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

Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150-mg scored tablets.<sup>27,28</sup>

Both emtricitabine and lamivudine have antiviral activity and efficacy against hepatitis B virus. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, please see the [Pediatric OI Guidelines](#).

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## Stavudine (d4T, Zerit) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Powder for Oral Solution:** 1 mg/mL

**Capsules:** 15 mg, 20 mg, 30 mg, and 40 mg

#### Generic Formulations

Powder for Oral Solution: 1 mg/mL

Capsules: 15 mg, 20 mg, 30 mg, and 40 mg

### Dosing Recommendations

**Note:** Stavudine **is no longer recommended** for use in children by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV, because it causes higher rates of adverse effects than other nucleoside reverse transcriptase inhibitors (NRTIs).

#### Pediatric (Aged $\geq 14$ 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>

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# Tenofovir Alafenamide (TAF, Vemlidy) (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: 25 mg<sup>a</sup>**

### Fixed-Dose Combination Tablets

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

## Dosing Recommendations

### [Descovy] Emtricitabine plus TAF

*Pediatric, Adolescent (Weighing  $\geq 25$  kg), and Adult Dose:*

- *Body Weight 25 to  $<35$  kg:* 1 tablet once daily in combination with other antiretroviral (ARV) agents, except for protease inhibitors (PIs) that require a CYP3A inhibitor (i.e., emtricitabine/TAF [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:* 1 tablet once daily in combination with an INSTI, NNRTI, or boosted PI.

### [Genvoya] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

*Pediatric, Adolescent (Weighing  $\geq 25$  kg), and Adult Dose:*

- 1 tablet once daily with food in ARV-naive patients. This dose of Genvoya can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA  $<50$  copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

### [Odefsey] Emtricitabine plus Rilpivirine plus TAF

*Pediatric, Adolescent (Weighing  $\geq 35$  kg), and Adult Dose:*

- 1 tablet once daily with a meal in ARV-naive patients with HIV-1 RNA  $\leq 100,000$  copies per mL. This dose of Odefsey can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 RNA

## Selected Adverse Events

- Asthenia, headache, diarrhea, nausea
- Increased serum lipids

## Special Instructions

- Measure serum creatinine before starting a TAF-containing regimen.
- Screen patients for hepatitis B virus (HBV) infection before using TAF. Severe acute exacerbation of HBV infection can occur when TAF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TAF is stopped.
- When using fixed-dose combination (FDC) tablets, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC (see the [Emtricitabine](#), [Elvitegravir](#), [Cobicistat](#), [Rilpivirine](#), and [Bictegravir](#) sections).
- Use of Genvoya is not FDA-recommended with other ARV drugs, but this FDC has safely been used with darunavir.<sup>1</sup> Descovy can be safely used with cobicistat- or ritonavir-boosted darunavir or atazanavir in patients weighing  $\geq 35$  kg.<sup>2</sup>
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or PIs co-formulated with cobicistat.
- When using Odefsey, patients must be able to take it with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal) because it contains rilpivirine.

## Metabolism/Elimination

- TAF undergoes renal excretion.

<50 copies per mL) for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Odefsey.

### **[Biktarvy] Bictegravir plus Emtricitabine plus TAF**

#### **Pediatric/Adolescent Dose (Aged <18 Years):**

- Biktarvy has not been Food and Drug Administration (FDA) approved for use in patients aged <18 years.
- *Children Aged <12 Years:* No data on appropriate dose of Biktarvy in children aged <12 years.
- *Children/Adolescents (Aged ≥12 Years to 18 Years and Weighing ≥35 kg):* 1 tablet once daily. This is an **investigational dose**.

#### **Adult Dose (Aged ≥18 Years):**

- 1 tablet once daily in ARV-naive patients. This Biktarvy dose can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.
- See the [Bictegravir](#) section for additional information.

#### **TAF Dosing in Patients with Renal Insufficiency:**

- The TAF 25-mg tablet<sup>a</sup> **is not recommended** for use in patients with estimated creatinine clearance (CrCl) <15 mL/min. TAF-containing co-formulations **are not recommended** in patients with estimated CrCl <30 mL/min.
- TAF-containing formulations do not require dose adjustment in patients with mild or moderate hepatic impairment, but should not be used in patients with severe hepatic impairment because they have not been studied in that group.

<sup>a</sup> 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.

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

- **Metabolism:** Tenofovir alafenamide (TAF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein (P-gp) and 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> Coadministration of TAF with rifamycins is not recommended.<sup>3</sup>
- Genvoya contains [elvitegravir](#) and [cobicistat](#) in addition to TAF. Elvitegravir is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by UGT1A1/3, and by oxidative metabolism pathways. Elvitegravir is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits adenosine triphosphate-dependent transporters BCRP and P-gp and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions when using both elvitegravir and cobicistat.
- **Absorption:** Administering elvitegravir and bictegravir concurrently with antacids lowers plasma concentrations of these antiretroviral (ARV) drugs. This is due to formation of complexes in the gastrointestinal tract, and not because of changes in gastric pH. Administration of Genvoya (which contains elvitegravir) or Biktarvy (which contains bictegravir) should be separated from administration of antacids by at least 2 hours, but preferably 4 hours. Chelation by high concentrations of divalent cations, such as iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and bictegravir. Because of this, Genvoya or Biktarvy should be administered at least 4 hours

before or after iron supplements or multivitamins containing iron.

- Odefsey contains [rilpivirine](#), which is a CYP3A substrate and requires dose adjustments when administered with CYP3A-modulating medications.
- Before Genvoya, Odefsey, [Descovy](#), or [Biktarvy](#) 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 could reduce clearance of TAF or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided when using Genvoya.
- *Protease inhibitors*: Genvoya should not be administered concurrently with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A metabolism.

### Major Toxicities

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

### Resistance

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

### Pediatric Use

#### Approval

[Descovy](#), a fixed-dose combination (FDC) drug that contains emtricitabine and TAF (FTC/TAF), is Food and Drug Administration (FDA)-approved for use in children aged  $\geq 6$  years and weighing  $\geq 25$  kg when used as part of an antiretroviral therapy regimen that does not include a ritonavir- or cobicistat-boosted protease inhibitor (PI). [Descovy](#) is FDA-approved for use in children aged  $\geq 6$  years and weighing  $\geq 35$  kg when used in combination with any antiretroviral (ARV) drugs, including ritonavir- or cobicistat-boosted PIs. [Odefsey](#), an FDC containing TAF, emtricitabine, and rilpivirine (TAF/FTC/RPV), is FDA-approved for use in children weighing  $\geq 35$  kg. [Genvoya](#), an FDC containing elvitegravir, cobicistat, emtricitabine, and TAF (EVG/COBI/FTC/TAF), is FDA-approved for use in children aged  $\geq 6$  years and weighing  $\geq 25$  kg when used as the single-tablet regimen without other ARVs (Table A). [Bictegravir](#) is only available as part of the FDC [Biktarvy](#), which contains bictegravir, emtricitabine, and TAF (BIC/FTC/TAF). [Biktarvy](#) is not FDA-approved for use in children or adolescents, but it was reported to be safe and effective in a small study in adolescents.<sup>4</sup>

TAF has antiviral activity and efficacy against hepatitis B virus (HBV). Testing for HBV should be performed prior to starting TAF treatment. 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 Infections Guidelines](#). TAF [alone \(as Vemlidy\)](#) is FDA-approved for use in persons aged  $\geq 8$  years, and is only approved for treating HBV, not HIV.

### Formulations

TAF-containing pills are smaller than their tenofovir disoproxil fumarate (TDF)-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills. TAF is available as the coformulated tablets FTC/TAF,<sup>2</sup> [FTC/RPV/TAF](#),<sup>3</sup> [EVG/COBI/FTC/TAF](#),<sup>6</sup> and [BIC/FTC/TAF](#)<sup>7</sup> ([Descovy](#), [Odefsey](#), [Genvoya](#), and [Biktarvy](#), respectively). [EVG/COBI/FTC/TAF \(Genvoya\)](#) contains TAF 10 mg while [FTC/TAF](#), [FTC/RPV/TAF](#), and [BIC/FTC/TAF \(Descovy, Odefsey, and Biktarvy, respectively\)](#) contain TAF 25 mg. Cobicistat boosts TAF blood concentrations and tenofovir diphosphate (TFV-DP) intracellular exposure after TAF administration. Therefore, administration of [EVG/COBI/FTC/TAF \(Genvoya\)](#), which contains TAF 10 mg and cobicistat, achieves TFV-DP systemic exposure that is similar to the exposure achieved by [FTC/RPV/TAF \(Odefsey\)](#) or [BIC/FTC/TAF \(Biktarvy\)](#), which contain TAF 25 mg but no cobicistat.

**Table A. FDA-Approved TAF-Containing Formulations**

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

<sup>a</sup> See [Bictegravir](#) section for information about investigational use in children and adolescents aged 12–18 years and weighing  $\geq 35$  kg.

**Key to Acronyms:** ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; EVG = elvitegravir; FTC = emtricitabine; HBV = hepatitis B virus; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine; TAF = tenofovir alafenamide

### Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate

Both TDF and TAF are prodrugs of the nucleotide reverse transcriptase inhibitor tenofovir (TFV). After oral administration, TDF is well absorbed<sup>8,9</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>10</sup> TFV is the main compound measurable in plasma after TDF administration. From the bloodstream, TFV enters cells and is phosphorylated to the active agent TFV-DP.

TAF<sup>11</sup> also has good oral bioavailability.<sup>12</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>13</sup> Once inside the cell, TAF is hydrolyzed to TFV,<sup>14,15</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>11</sup> Therefore, a much lower dose of TAF results in intracellular concentrations of TFV-DP that are equivalent or higher than the concentrations seen after TDF administration.

The key pharmacokinetic 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>13</sup> Because it is intracellular TFV-DP that suppresses viral replication, TAF should have antiviral efficacy equivalent to TDF, but should avoid the toxicities that are specifically related to plasma TFV. High plasma TFV concentration has been linked to TDF-related endocrine disruption that is associated with low bone mineral density (BMD).<sup>16</sup> **High plasma TFV has also been closely associated** with both glomerular<sup>16,17</sup> and proximal tubular<sup>18</sup> renal toxicity.

**Table B. Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV:<sup>a</sup> TAF versus TDF<sup>13</sup>**

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> ( $\mu$ M*h)	3.5 (77.1)	3.0 (119.6)

<sup>a</sup> Mean age 38 years; range 20–57 years

**Note:** Data are mean (% coefficient of variation), tau is the dosing interval (i.e., 24 hours), and C<sub>max</sub> is the maximum concentration.

**Key to Acronyms:** AUC = area under the curve; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TFV-DP = tenofovir diphosphate

### Tenofovir Alafenamide Efficacy in Clinical Trials in Adults and Adolescents

In adults, TAF is noninferior to TDF over 48 **to 96** weeks in its ability to control viral load when used in

combination with elvitegravir, cobicistat, and emtricitabine;<sup>19-22</sup> with emtricitabine and rilpivirine;<sup>23</sup> with darunavir, cobicistat, and emtricitabine;<sup>24</sup> and when TAF and emtricitabine are administered in combination with other ARV drugs.<sup>25</sup> The combination of TAF, elvitegravir, cobicistat, and emtricitabine has been shown to have similar efficacy when used in adults and two groups of children: those aged  $\geq 12$  years and weighing  $\geq 35$  kg<sup>26</sup> and those aged  $\geq 6$  years and weighing  $\geq 25$  kg.<sup>27</sup>

## Pharmacokinetics

### Drug Exposure and Virologic Response

Virologic suppression is most closely related to intracellular TFV-DP concentrations. At clinically meaningful doses, TAF generates peripheral blood mononuclear cell TFV-DP concentrations in adults that are about seven-fold higher than those generated with TDF.<sup>13,19</sup> Higher TFV-DP concentrations result in a stronger antiviral potency<sup>13</sup> and a higher barrier to resistance.<sup>28,29</sup> Therefore, compared to TDF, TAF may have a potentially enhanced ability to maintain effectiveness with nucleoside reverse transcriptase inhibitor (NRTI)-resistant virus. 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>26</sup>

### Drug Exposure and Safety: All Age Groups

FTC/TAF (Descovy) can be safely combined with dolutegravir or raltegravir without concern for drug interactions. Emtricitabine and TAF have also safely been combined with bicitgravir in the fixed-dose combination Biktarvy.

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

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

Regimen	TAF AUC <sup>a</sup>	TAF AUC Ratio TAF Containing Regimen/ Genvoya (10 mg TAF) Adult Exposure	TFV AUC <sup>a</sup>	TFV AUC Ratio TFV Containing Regimen/ Stribild (300 mg TDF) Adult Exposure
<b>Adult</b>				
Stribild (EVG/COBI/FTC/TDF 300 mg)	N/A	N/A	4,400	1.00
Genvoya (EVG/COBI/FTC/TAF 10 mg)	210	1.0	290	0.07
DRV/r plus TAF 25 mg <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 for ages 12–18 years	N/A	N/A	6,028	1.37
Genvoya for ages 12–18 years	200	0.95	290	0.07
Genvoya 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 using 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 tenofovir alafenamide, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/208215Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000SumR.pdf) and from the tenofovir alafenamide clinical pharmacology review, available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/208215Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208215Orig1s000ClinPharmR.pdf), using data from the Stribild product label (FDA 2017 August) and Genvoya product label (FDA 2017 September)

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

Clinical trials in adults showing the safety of emtricitabine/TAF administered with ritonavir-boosted atazanavir or ritonavir-boosted darunavir have used emtricitabine/TAF 200 mg/10 mg, a formulation not available in the United States.<sup>30</sup> The FDA states that when emtricitabine/TAF 200 mg/25 mg (Descovy) is combined with cobicistat- or ritonavir-boosted atazanavir, darunavir, or lopinavir in adults, “no clinically significant drug interactions have been observed or are expected,” so the combination of emtricitabine/TAF (Descovy) is FDA-approved for adults independent of the accompanying ARVs (which may include a boosted PI or an INSTI).<sup>2</sup> Moreover, in Trial 299-0102, a Phase 2b trial in adults comparing a regimen of darunavir/cobicistat (DRV/c) plus emtricitabine/TAF 10 mg to a regimen of DRV/c plus emtricitabine/TDF, there was a concern of worse Week 48 virologic outcome for the TAF 10 mg arm. Hence, emtricitabine/TAF 25 mg was recommended for approval instead of emtricitabine/TAF 10 mg.<sup>31</sup> This is not the case in Canada or Europe, where emtricitabine is combined with TAF 10 mg in an FDC and used in combination with boosted PIs.

#### *Drug Exposure and Safety: Aged 12 Years to 18 Years and Weighing $\geq 35$ kg*

Studies of EVG/COBI/FTC/TAF (Genvoya) in children aged 12 to 18 years and weighing  $\geq 35$  kg showed that drug exposures were similar to those found in adults (Table C), and that the drug was well tolerated and efficacious over 48 weeks of study.<sup>26</sup> Since these drug exposures were similar to those seen in adults, emtricitabine/TAF was also FDA-approved for 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 bicitegravir 50 mg, emtricitabine 200 mg, and TAF 25 mg) was administered to youths aged 12 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 of the 24 participants had viral loads <50 copies/mL at 24 weeks.<sup>4</sup>

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

Studies of EVG/COBI/FTC/TAF (Genvoya) in children aged 6 to <12 years and weighing  $\geq 25$  kg showed that drug exposures were somewhat higher than those found in adults (Table C), but the drug was well tolerated and efficacious over 24 weeks of study.<sup>27,32</sup> This led to FDA approval of Genvoya for children aged  $\geq 6$  years who weigh  $\geq 25$  kg.<sup>6</sup>

Because integrase inhibitors do not increase TAF concentrations, regimens of FTC/TAF 25 mg (Descovy) plus an INSTI are expected to result in safe drug exposures that are similar to those seen with the single-tablet regimen EVG/COBI/FTC/TAF 10 mg (Genvoya). This led the FDA to approve Descovy for children aged  $\geq 6$  years and weighing  $\geq 25$  kg when used in combination with other ARVs that do not include a boosted PI.<sup>2</sup>

Because cobicistat- or ritonavir-boosted atazanavir, darunavir, or lopinavir increase the TAF exposure to higher concentrations than those seen with use of EVG/COBI/FTC/TAF (Genvoya), and because there are no data on this combination in children weighing <35 kg, the safety of FTC/TAF (Descovy) combined with cobicistat- or ritonavir-boosted PIs in children with body weights between 25 kg and <35 kg cannot be assured. That is why the FDA approval for Descovy in combination with boosted PIs is limited to children weighing  $\geq 35$  kg (Table A).<sup>2</sup>

### **Toxicity**

#### *Bone*

TAF causes bone toxicity less frequently than TDF.<sup>19-21,24,25</sup> For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/COBI/FTC/TAF had a smaller decrease in BMD at the spine (mean change  $-1.30\%$  vs.  $-2.86\%$ ;  $P < 0.0001$ ) and hip ( $-0.66\%$  vs.  $-2.95\%$ ;  $P < 0.0001$ ) at 48 weeks than those given EVC/COBI/FTC/TDF.<sup>19</sup> These differences were maintained to 96 weeks.<sup>22</sup>

#### *Renal*

Studies in adolescents aged 12 to 17 years<sup>26</sup> and adults<sup>19-21,24,25</sup> show that TAF is less frequently associated with glomerular and renal tubular damage than TDF. For example, in one study of 1,733 randomized adult participants with HIV, those treated with EVG/COBI/FTC/TAF had a smaller mean increase in serum

creatinine (0.08 vs. 0.12 mg/dL;  $P < 0.0001$ ) than those given EVC/COBI/FTC/TDF, and a smaller percent change from baseline in urine protein to creatinine ratio (median % change -3% vs. +20%;  $P < 0.0001$ ) at 48 weeks.<sup>19</sup> These differences persisted to 96 weeks of follow-up.<sup>22</sup> Safety of EVG/COBI/FTC/TAF has been shown in adults with estimated creatinine clearance between 30 and 69 mL/min.<sup>33</sup> For TAF, less intense renal safety monitoring may be needed than with TDF, but more experience with the drug in broad clinical practice will be needed before a specific recommendation can be made.

### Lipids

In treatment-naïve adults evaluated after 48 weeks of therapy, the initiation of elvitegravir/cobicistat/emtricitabine/TAF was associated with increases in serum lipids greater than those observed with the initiation of elvitegravir/cobicistat/emtricitabine/TDF, with a mean increase in total cholesterol of 31 mg/dL versus 23 mg/dL and low-density lipoprotein (LDL) cholesterol levels of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents treated with elvitegravir/cobicistat/emtricitabine/TAF, median changes from baseline to Weeks 24 and 36 were the following: fasting total cholesterol increased 26 mg/dL and 36 mg/dL, respectively; fasting direct LDL increased 10 mg/dL and 17 mg/dL, respectively; and fasting triglycerides increased 14 mg/dL and 19 mg/dL, respectively.<sup>34</sup> Monitoring serum lipids while the patient is taking **TAF-containing FDCs** is warranted, given these data. For more information, see the [Dyslipidemia section](#).

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# Tenofovir Disoproxil Fumarate (TDF, Viread) (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 Powder:** 40 mg per 1 g of oral powder (1 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

- [Truvada low-strength tablet]
  - Emtricitabine 100 mg plus tenofovir disoproxil fumarate (TDF) 150 mg
  - Emtricitabine 133 mg plus TDF 200 mg
  - Emtricitabine 167 mg plus TDF 250 mg
- [Truvada tablet] Emtricitabine 200 mg plus TDF 300 mg
- [Atripla] Efavirenz 600 mg plus emtricitabine 200 mg plus TDF 300 mg
- [Complera] Emtricitabine 200 mg plus rilpivirine 25 mg plus TDF 300 mg
- [Stribild] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus TDF 300 mg
- [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus TDF 300 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Not Food and Drug Administration-approved or recommended for use in neonates and infants aged <2 years.

### Child (Aged ≥2 Years to <12 Years) Dose:<sup>a</sup>

- 8 mg/kg/dose once daily

### TDF Oral Powder Dosing Table

Body Weight	TDF Oral Powder Once-Daily Scoops of Powder
10 kg to <12 kg	2 scoops (80 mg)
12 kg to <14 kg	2.5 scoops (100 mg)
14 kg to <17 kg	3 scoops (120 mg)
17 kg to <19 kg	3.5 scoops (140 mg)
19 kg to <22 kg	4 scoops (160 mg)
22 kg to <24 kg	4.5 scoops (180 mg)
24 kg to <27 kg	5 scoops (200 mg)
27 kg to <29 kg	5.5 scoops (220 mg)
29 kg to <32 kg	6 scoops (240 mg)
32 kg to <34 kg	6.5 scoops (260 mg)
34 kg to <35 kg	7 scoops (280 mg)
≥35 kg	7.5 scoops (300 mg)

## Selected Adverse Events

- Asthenia, headache, diarrhea, nausea, vomiting, flatulence
- Renal insufficiency, proximal renal tubular dysfunction that may include Fanconi syndrome
- Decreased bone mineral density<sup>a</sup>

## Special Instructions

- Do not crush tablets; TDF oral powder formulation is available for patients unable to swallow tablets.
- TDF oral powder should be measured only with the supplied dosing scoop: 1 level scoop = 1 g powder = 40 mg TDF.
- Mix TDF oral powder in 2 to 4 oz of soft food that does not require chewing (e.g., applesauce, yogurt). Administer immediately after mixing to avoid the bitter taste.
- Do not try to mix the TDF oral powder with liquid. The powder may float on the top even after vigorous stirring.
- Although TDF can be administered without regard to food, food requirements vary depending on the other ARV drugs contained

### TDF Tablet Dosing Table for Patients Aged $\geq 2$ Years and Weighing $\geq 17$ 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
$\geq 35$ kg	300 mg

#### Adolescent (Weighing $\geq 35$ kg)<sup>a</sup> and Adult Dose:

- TDF 300 mg once daily

#### [Truvada] Emtricitabine plus TDF (FTC/TDF)

*Pediatric Dose:*

#### Truvada Pediatric Dosing Table

Body Weight	FTC/TDF Tablet Once Daily
17 kg to <22 kg	1 FTC/TDF 100 mg/150 mg tablet
22 kg to <28 kg	1 FTC/TDF 133 mg/200 mg tablet
28 kg to <35 kg	1 FTC/TDF 167 mg/250 mg tablet
$\geq 35$ kg	1 FTC/TDF 200 mg/300 mg tablet

*Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- 1 FTC/TDF 200 mg/300 mg tablet once daily

#### [Atripla] Efavirenz plus Emtricitabine plus TDF

*Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:*

- 1 tablet once daily

#### [Complera] Emtricitabine plus Rilpivirine plus TDF

*Adolescent (Weighing  $\geq 35$  kg) and Adult Dose:*

- 1 tablet once daily in treatment-naïve adults with baseline viral load <100,000 copies/mL or virologically suppressed adults who are currently on their first or second regimen and have no history of virologic failure or resistance to rilpivirine and other antiretroviral (ARV) drugs.
- Administer with a meal of at least 500 calories.

#### [Stribild] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF

*Adolescent (Weighing >35 kg with a Sexual Maturity Rating of 4 or 5) and Adult Dose:*

- 1 tablet once daily in treatment-naïve adults. This dose of Stribild can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known

in a FDC tablet. Food requirements are listed with dosing recommendations.

- Measure serum creatinine and urine dipstick for protein and glucose before starting a TDF-containing regimen and monitor serum creatinine and urine dipstick for protein and glucose at intervals (see [Table 15i](#)) during continued therapy. Measure serum phosphate if there is clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before using TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, in patients with HBV infection, monitor hepatic function and hepatitis B viral load for several months after therapy with TDF is stopped.
- When using FDC tablets, see other drug sections for special instructions and additional information about the individual drug components.
- Tenofovir alafenamide (TAF) has less bone and renal toxicity than TDF, but equal antiviral efficacy. Do not use TAF and TDF together. Consider switching from TDF to TAF in appropriate clinical settings.

### Metabolism/Elimination

- TDF is renally excreted.

#### TDF Dosing in Patients with Renal Insufficiency:

- TDF dose should be decreased in patients with impaired renal function (creatinine clearance [CrCl] <50 mL/min). Consult manufacturer's prescribing information for adjustment of dose in accordance with CrCl.
- The FDCs Atripla, Complera, and Symfi Lo should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- The FDC Truvada should not be used in patients with CrCl <30 mL/min or in patients requiring 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.

substitutions associated with resistance to the individual components of Stribild.

- Administer with food.

#### **[Symfi Lo] Efavirenz plus Lamivudine plus TDF**

*Pediatric (Weighing  $\geq 35$  kg) and Adult Dose:*

- 1 tablet once daily

**Note:** The new fixed-dose combination (FDC) Symfi Lo, which has a lower dose of efavirenz, has not yet been discussed by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel). The Panel will address its use in children in a later update.

<sup>a</sup> See text for concerns about decreased bone mineral density, especially in prepubertal patients and those in early puberty (**Sexual Maturity Rating** 1 and 2, **previously called** Tanner staging).

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

- Tenofovir disoproxil fumarate (TDF) is a substrate of the adenosine triphosphate-dependent transporters P-glycoprotein (P-gp) and breast cancer resistance protein. When TDF is co-administered 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)**.
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations increase when the drug is co-administered with TDF, and this combination **should not be used** because of increase in didanosine toxicity.
- *Protease inhibitors:* Because TDF decreases atazanavir plasma concentrations, atazanavir without ritonavir **should not be co-administered** with TDF. In addition, the combination of atazanavir and lopinavir/ritonavir increases plasma tenofovir concentrations and potentiates 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, and 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 is Food and Drug Administration (FDA)-approved for use in children aged  $\geq 2$  years when used as a component of antiretroviral therapy (ART).

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

### ***Efficacy in Clinical Trials in Adults Compared to Children and Adolescents***

The standard adult dose 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 years to 12 years, the FDA-approved dose is TDF 8 mg/kg/dose administered once daily, which closely approximates the dose of TDF 208 mg/m<sup>2</sup>/dose used in early studies in children.<sup>3</sup>

In adults, the recommended TDF dose is highly effective. In comparative clinical trials in adults, TDF administered with lamivudine or emtricitabine as a dual-NRTI backbone in combination with efavirenz had better viral efficacy than zidovudine used with lamivudine and efavirenz.<sup>4-6</sup> TDF administered with emtricitabine has been compared to abacavir administered with lamivudine in several adult studies and meta-analyses, with variable results.<sup>7-11</sup>

In children, the published efficacy data for TDF are mixed, but potency equal to that in adults is seen in pediatric patients aged 3 years to 18 years with susceptible virus. In children aged 2 years to  $< 12$  years, TDF 8 mg/kg/dose once daily was noninferior to twice-daily zidovudine- or stavudine-containing ART over 48 weeks of randomized treatment.<sup>12,13</sup> Virologic success is lower in treatment-experienced patients with extensive drug resistance.<sup>14-16</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>17</sup> A modeling study suggests that children and adolescents treated with TDF may have higher intracellular TFV-DP concentrations than adults,<sup>18</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>3,19,20</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 if it is allowed to sit too long.

### ***Toxicity***

#### ***Bone Toxicity***

TDF administration is associated with decreased BMD in both adults<sup>21,22</sup> and children.<sup>13,23-25</sup> When treated with TDF, younger children with **Sexual Maturity Ratings (SMRs; previously Tanner Stages)** 1 and 2 may be at higher risk of decreased BMD than children with more advanced pubertal development (i.e., SMR  $\geq 3$ ).<sup>19</sup> Discontinuation of TDF results in partial or complete recovery of BMD.<sup>23</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>14</sup>

TDF administration disrupts vitamin D metabolism,<sup>26,27</sup> and the decrease in BMD associated with TDF initiation was attenuated in adults with co-administration of high doses of vitamin D3 (4000 International Units [IU] daily) and calcium carbonate (1000 mg daily) for the first 48 weeks of TDF treatment.<sup>28</sup> During chronic TDF administration, youth with HIV who received vitamin D3 supplements (50,000 IU once monthly) had decreased serum parathyroid hormone<sup>29</sup> and increased lumbar spine BMD.<sup>27</sup> The serum 25-hydroxy vitamin D concentration in the group with improved BMD was 37 ng/mL. Since this improvement in lumbar spine BMD was seen in patients with and without baseline vitamin D deficiency, some practitioners recommend vitamin D supplementation in all patients treated with TDF-containing ART.

Plasma concentrations of the TDF metabolite plasma TFV have been associated with TDF-related endocrine disruption and low BMD.<sup>26</sup> Tenofovir alafenamide (TAF), which is associated with lower plasma TFV concentrations than TDF, causes less decline in BMD than TDF (see the [Tenofovir Alafenamide](#) section for more information). Consider switching from TDF to TAF in appropriate clinical settings.

#### *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 treated with TDF. Given the potential for BMD loss in children treated with TDF, some experts obtain a DXA before initiation of TDF therapy and approximately 6 months after starting TDF, especially in prepubertal patients and those early in puberty (i.e., SMR 1 and 2). If DXA results are abnormal, consider referral to a subspecialist in pediatric endocrinology or a related field.

Despite the ease of use of a once-daily drug and the efficacy of TDF, the potential for BMD loss during the important period of rapid bone accrual in childhood and early adolescence is concerning and favors use of abacavir or TAF in children with SMRs 1 to 3, because children with perinatally acquired HIV are at risk for low peak bone mass.<sup>30,31</sup>

#### *Renal Toxicity*

New onset or worsening of renal impairment has been reported in adults<sup>32</sup> and children<sup>33,34</sup> receiving TDF. In one study, renal toxicity led to discontinuation of TDF in 3.7% of children with HIV (6/159 children) who were treated with TDF.<sup>16</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>32,33</sup> Irreversible renal failure is quite rare, but cases have been reported.<sup>35</sup>

The main target of TDF nephrotoxicity is the renal proximal tubule.<sup>33</sup> Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.<sup>36,37</sup>

Subclinical renal tubular damage is more common than clinically apparent renal tubular injury. Increased urinary beta-2 microglobulin was identified in 27% of children (12/44 children) treated with TDF and in 4% of children (2/48 children) not treated with TDF.<sup>38</sup> The risks of TDF-associated proteinuria and chronic kidney disease increase with the duration of treatment.<sup>39,40</sup> Of 89 participants aged 2 years to 12 years who received TDF in Gilead Study 352 (where participants had a median drug exposure of 104 weeks), four participants were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.<sup>12</sup>

Plasma TFV is the TDF metabolite most closely associated with both glomerular<sup>26,41</sup> and proximal tubular<sup>42</sup> toxicity. TAF, which generates lower plasma TFV concentrations than TDF, is associated with less renal toxicity than TDF (see the [Tenofovir Alafenamide](#) section).

#### *Monitoring Potential Renal Toxicity*

Because TDF has the potential to decrease creatinine clearance and cause renal tubular dysfunction, the Panel recommends measuring serum creatinine and using a urine dipstick to check protein and glucose levels prior to drug initiation. It is unclear how often creatinine and renal tubular function (urine protein and glucose)

should be monitored in asymptomatic patients. Many Panel members monitor creatinine with other blood tests every 3 to 4 months and perform urinalysis every 6 to 12 months. Serum phosphate should be measured if clinically indicated; renal phosphate loss can occur in the presence of normal creatinine and the absence of proteinuria. Because nephrotoxicity increases with the duration of TDF treatment, monitoring should be continued during long-term therapy with the drug.

Because renal glomerular damage primarily increases the urine concentration of albumin, and proximal renal tubular damage increases urine concentrations of low-molecular-weight proteins like beta-2 microglobulin, dipstick urinalysis (measuring primarily urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measuring urine albumin and urine protein and calculating the urine albumin to urine protein ratio can be helpful in identifying the nonalbumin proteinuria that is seen in TDF-associated nephrotoxicity.<sup>43,44</sup> While these more complex and expensive tests may be used in research settings, in clinical practice, renal tubular damage is perhaps easiest to identify by using a renal dipstick to identify normoglycemic glycosuria and proteinuria.

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# Zidovudine (ZDV, AZT, Retrovir) (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

**Tablets:** 300 mg

**Syrup:** 10 mg/mL

**Concentrate for Injection or Intravenous Infusion:** 10 mg/mL

### Generic Formulations:

Zidovudine capsules, tablets, syrup, and injection are approved by the Food and Drug Administration for manufacture and distribution in the United States.

### Fixed-Dose Combination Tablets:

- [*Combivir and Generic*] Lamivudine 150 mg plus zidovudine 300 mg (scored)
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

## Dosing Recommendations

**Note:** See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#) for information about using zidovudine to prevent perinatal transmission.

### Recommended Neonatal Dose for Treatment of HIV by Gestational Age (Weeks) at Birth<sup>a</sup>

Gestational Age at Birth	Oral Zidovudine Dose								
≥35 Weeks	Birth to Age 4 Weeks: <ul style="list-style-type: none"><li>• 4 mg/kg orally twice daily or alternative simplified weight band dosing</li></ul>								
	Simplified Weight Band Dosing for Infants with a Gestational Age ≥35 Weeks at Birth: <b>Note:</b> The doses in this table provide approximately 4 mg/kg orally twice daily from birth to age 4 weeks.								
	<table border="1"><thead><tr><th>Weight Band</th><th>Volume Zidovudine 10 mg/mL Oral Syrup Twice Daily</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>	Weight Band	Volume Zidovudine 10 mg/mL Oral Syrup Twice Daily	2 kg to <3 kg	1 mL	3 kg to <4 kg	1.5 mL	4 kg to <5 kg	2 mL
	Weight Band	Volume Zidovudine 10 mg/mL Oral Syrup Twice Daily							
	2 kg to <3 kg	1 mL							
3 kg to <4 kg	1.5 mL								
4 kg to <5 kg	2 mL								
Aged >4 Weeks: <ul style="list-style-type: none"><li>• 12 mg/kg orally twice daily</li></ul>									

## Selected Adverse Events

- Bone marrow suppression: macrocytosis with or without anemia, neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Lipodystrophy and lipoatrophy
- Myopathy (associated with prolonged use of zidovudine) and myositis

## Special Instructions

- Give zidovudine without regard to food.
- If substantial granulocytopenia or anemia develops in patients receiving zidovudine, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells.
- For infants unable to tolerate oral agents, the intravenous (IV) dose should be 75% of the oral dose, but the dosing interval should remain the same.
- When using fixed-dose combination (FDC) tablets that contain zidovudine, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

Gestational Age at Birth	Oral Zidovudine Dose
≥30 to <35 Weeks	<p>Birth to Age 2 Weeks:</p> <ul style="list-style-type: none"> <li>• 2 mg/kg orally twice daily</li> </ul> <p>Aged 2 Weeks to 6 to 8 Weeks:</p> <ul style="list-style-type: none"> <li>• 3 mg/kg orally twice daily</li> </ul> <p>Aged &gt;6 to 8 Weeks:</p> <ul style="list-style-type: none"> <li>• 12 mg/kg orally twice daily</li> </ul>
<30 Weeks	<p>Birth to Age 4 Weeks:</p> <ul style="list-style-type: none"> <li>• 2 mg/kg orally twice daily</li> </ul> <p>Aged 4 Weeks to 8 to 10 Weeks:</p> <ul style="list-style-type: none"> <li>• 3 mg/kg orally twice daily</li> </ul> <p>Aged &gt;8 to 10 Weeks:</p> <ul style="list-style-type: none"> <li>• 12 mg/kg orally twice daily</li> </ul>

<sup>a</sup> For premature infants who are diagnosed with HIV, the time to change the dose to continuation dose varies with postgestational age and clinical status of the neonate (see the Special Issues for Neonates section below).

**Note:** For infants who are unable to tolerate oral agents, the intravenous (IV) dose should be 75% of the oral dose, but the dosing interval should remain the same.

### Infant (Aged ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery, Weighing ≥4 kg) and Child Dose

#### Zidovudine Weight-Based Dosing

Body Weight	Twice-Daily Dosing
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

#### Alternative Body Surface Area Dosing

- Oral: 180–240 mg/m<sup>2</sup> body surface area every 12 hours

#### Adolescent (Aged ≥18 Years) and Adult Dose:

- 300 mg twice daily

#### [Combivir and Generic] Lamivudine plus Zidovudine

Adolescent (Weighing ≥30 kg) and Adult Dose:

- 1 tablet twice daily

#### [Trizivir] Abacavir plus Lamivudine plus Zidovudine

Adolescent (Weighing ≥40 kg) and Adult Dose:

- 1 tablet twice daily

## Metabolism/Elimination

- Metabolized primarily in the liver to zidovudine glucuronide, which is renally excreted.
- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.

#### Zidovudine Dosing in Patients with Renal Impairment:

- Dose adjustment is required in renal insufficiency.

#### Zidovudine Dosing in Patients with Hepatic Impairment:

- Dose may need to be reduced in patients with hepatic impairment.
- Do not use FDC products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min or in patients who are on dialysis or who have impaired hepatic function.

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

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine **should not be administered in combination** with stavudine because of *in vitro* virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents, including ganciclovir, valganciclovir, interferon alfa, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine.
- *Nucleoside analogues that affect DNA replication:* Nucleoside analogues, such as ribavirin, antagonize *in vitro* antiviral activity of zidovudine.
- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine should be avoided. Doxorubicin may inhibit the phosphorylation of zidovudine to its active form.

### **Major Toxicities**

- *More common:* Hematologic toxicity, including granulocytopenia and anemia, particularly in patients with advanced HIV-1 disease. Headache, malaise, nausea, vomiting, and anorexia. Neutropenia may occur more frequently in infants receiving both lamivudine and zidovudine than in infants receiving only zidovudine.<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:* Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study.<sup>2</sup> Possible increased risk of cardiomyopathy.<sup>3</sup> Possible association between first-trimester exposure to zidovudine and congenital heart defects (see [Teratogenicity](#) in the [Perinatal Guidelines](#)).<sup>4-6</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*

Zidovudine is frequently included as a component of the NRTI backbone for antiretroviral therapy (ART) and has been studied in children in combination with **other NRTIs, including** abacavir and lamivudine.<sup>7-23</sup> Pediatric experience with zidovudine both for treating HIV and for preventing perinatal transmission is extensive. **However, the mitochondrial toxicity of zidovudine leads many experts to favor the use of abacavir or tenofovir alafenamide in cases where patient age and the results of viral resistance testing do not restrict the use of these drugs.**

#### *Efficacy in Clinical Trials*

##### **Zidovudine in Combination with Other NRTIs**

- Zidovudine with lamivudine has been extensively studied in children and has been a part of ART regimens in many trials.
- Safety and efficacy of zidovudine combined with lamivudine was compared to abacavir/lamivudine and stavudine/lamivudine in children aged <5 years in the CHAPAS-3 study. All regimens also contained either nevirapine or efavirenz. All NRTIs had low toxicity and good clinical, immunologic, and virologic responses.<sup>24</sup>
- Zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in a European pediatric study.<sup>25,26</sup>

#### *Special Issues in Neonates*

Perinatal trial PACTG 076 established that zidovudine prophylaxis given to the mother during pregnancy, labor, and delivery, and given to the newborn reduced the risk of perinatal transmission of HIV by nearly 70%<sup>27</sup> (see [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) for further discussion

on the use of zidovudine for the prevention of perinatal transmission of HIV). Zidovudine 4 mg/kg body weight every 12 hours is recommended for neonates and infants with  $\geq 35$  weeks' gestation for prevention of perinatal HIV transmission. Infants who are HIV-exposed but uninfected should continue on the prophylactic dose for 4 to 6 weeks, depending on the assessment of risk for perinatal transmission and gestational age at time of delivery.

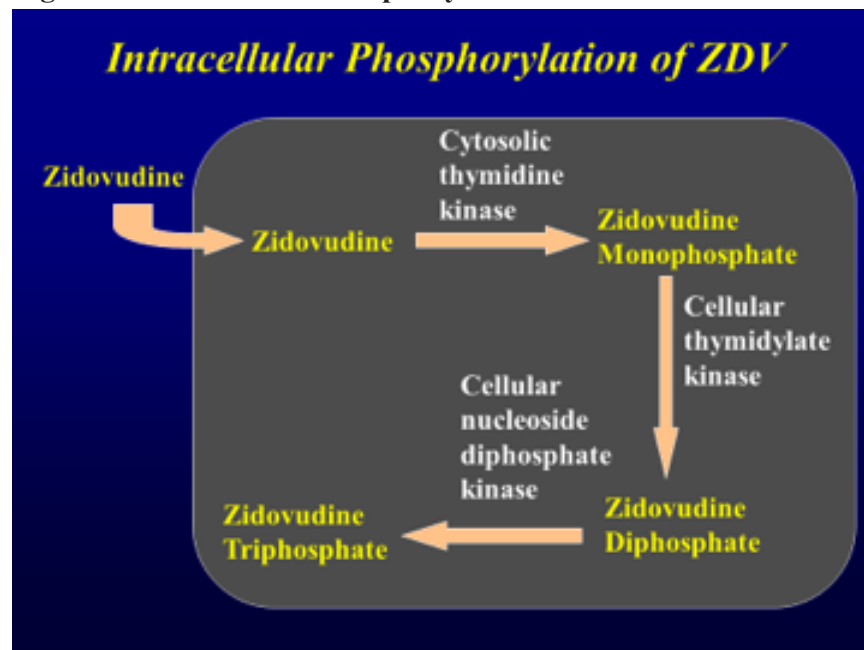
For full-term neonates who receive an HIV diagnosis, the zidovudine dose should be increased at age 4 weeks to the continuation dose (see dosing table). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically over the first 4 to 6 weeks of life in full-term neonates.

For premature infants who are diagnosed with HIV infection, the time to increase the dose from the initial dose varies with postgestational age and the clinical status of the neonate. On the basis of modeling and the pharmacokinetics (PK) of zidovudine in premature infants, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends switching to a dose of zidovudine 12 mg/kg twice daily at postgestational age 6 to 8 weeks in infants born at  $\geq 30$  to  $< 35$  weeks. For infants who are born at  $< 30$  weeks, change to zidovudine 12 mg/kg twice daily at a postgestational age of 8 to 10 weeks.<sup>28</sup> Careful clinical assessment of the infant, evaluation of hepatic and renal function, and review of concomitant medications should be performed prior to increasing the zidovudine dose to that recommended for full-term infants.

### Pharmacokinetics

Overall, zidovudine PK in pediatric patients aged  $> 3$  months are similar to those seen in adults. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing **is not recommended** because of the low intracellular zidovudine triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.<sup>29</sup> PK studies such as PACTG 331 demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with the clearance observed in term newborns of similar postnatal age.<sup>8</sup> Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease.<sup>19</sup>

**Figure A: Intracellular Phosphorylation of Zidovudine**



Source: Mirochnick, M. Antiretroviral pharmacology in pregnant women and their newborns. Presented at: Advances in Pediatric AIDS. 1999. Montreal, CA.

The rate-limiting step in phosphorylation of zidovudine to active zidovudine triphosphate is the limited amount of thymidylate kinase. Increasing doses of zidovudine will lead to increased zidovudine plasma concentrations

and increased intracellular concentrations of zidovudine monophosphate but not zidovudine diphosphate or zidovudine triphosphate. In 31 infants receiving zidovudine for prevention of perinatal transmission, intracellular zidovudine metabolites were measured after delivery. Plasma zidovudine and intracellular zidovudine monophosphate decreased by roughly 50% between postdelivery Day 1 and Day 28, whereas zidovudine diphosphate and zidovudine triphosphate remained low throughout the sampling period.<sup>30</sup> On the basis of poor correlation between zidovudine dose and intracellular zidovudine triphosphate concentrations, a simplified dosing approach can be used for infants  $\geq 35$  weeks gestation receiving approximately zidovudine 4 mg/kg twice daily oral dosing for the first 4 weeks of life (see the dosing table). These volumes provide approximately zidovudine 4 mg/kg per dose using the 10 mg/mL oral syrup. This approach should simplify the minor dose adjustments that are commonly made based on changes in infant weight during zidovudine use in the first 4 weeks of life. These changes in weight and small differences in zidovudine dose will have minor effects on the intracellular concentrations of zidovudine triphosphate. This approach should make it easier for caregivers to administer zidovudine oral syrup to their infants.

### **Toxicity**

Several studies suggest that the adverse hematologic effects of zidovudine may be concentration-dependent, with a higher risk of anemia and neutropenia in patients with higher mean area under the curve.<sup>7,8,31</sup>

Incidence of hematological toxicity was investigated in the ARROW study, which randomized Ugandan/Zimbabwean treatment-naïve children to receive either zidovudine-containing regimens or abacavir-containing regimens. The incidence of severe anemia was similar regardless of zidovudine use, and this finding suggests that advanced HIV disease contributed to low hemoglobin values. Zidovudine use was associated with severe neutropenia in a small number of children.<sup>32</sup>

Zidovudine is associated with greater mitochondrial toxicity when compared to abacavir and tenofovir disoproxil fumarate but less than stavudine.<sup>33,34</sup>

While the incidence of cardiomyopathy associated with perinatal HIV infection has decreased dramatically since use of ART became routine, a regimen containing zidovudine may increase the risk.<sup>3</sup> Recent analysis of data from a U.S.-based, multicenter, prospective cohort study (PACTG 219/219C) found that ongoing zidovudine exposure was independently associated with a higher rate of cardiomyopathy.<sup>3</sup>

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## **Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)**

Efavirenz (EFV, Sustiva)

Etravirine (ETR, Intelence, TMC 125)

Nevirapine (NVP, Viramune)

Rilpivirine (RPV, Edurant, TMC 278)

## Efavirenz (EFV, Sustiva) (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:** 50 mg, 200 mg

**Tablets:** 600 mg

#### Fixed-Dose Combination Tablets:

- [Atripla] Efavirenz 600 mg plus emtricitabine 200 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Symfi Lo] Efavirenz 400 mg plus lamivudine 300 mg plus TDF 300 mg

### Dosing Recommendations

#### Neonatal Dose:

- Efavirenz is not approved for use in neonates.

#### Pediatric Dose

- Efavirenz capsules can be opened and the contents used as a sprinkle preparation for infants and children who are unable to swallow capsules.

*Infants and Children Aged 3 Months to <3 Years and Weighing  $\geq$  3.5 kg:*

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) **does not recommend** the use of efavirenz in children aged 3 months to <3 years **due to highly variable pharmacokinetics in this age group.**
- **Note:** If the use of efavirenz is unavoidable due to a clinical situation, the Panel suggests using investigational doses of efavirenz in this age group (see investigational dosing [tables A1 and A2](#) in the [Pharmacokinetics and Dosing: Infants and Children Aged <3 Years](#) section below). Evaluation of CYP2B6 genotype is required prior to use in this age group. Therapeutic drug monitoring should be used with an efavirenz plasma concentration measured 2 weeks after initiation; some experts would also measure plasma concentration at age 3 years after making the transition to the new dose (see [Therapeutic Drug Monitoring](#) in the text below). For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

### Selected Adverse Events

- Rash, which is generally mild and transient and appears to be more common in children than in adults
- Central nervous system symptoms such as fatigue, poor sleeping patterns, **insomnia**, vivid dreams, impaired concentration, agitation, seizures, depression, suicidal ideation
- False-positive with some cannabinoid and benzodiazepine tests
- Gynecomastia
- Hepatotoxicity
- QTc prolongation has been observed with the use of efavirenz. Clinicians should consider using an alternative to efavirenz in patients taking a drug that has a known risk of Torsades de Pointes or in patients who are at higher risk of Torsades de Pointes.

### Special Instructions

- Efavirenz can be swallowed as a whole capsule/tablet or administered by sprinkling the contents of an opened capsule on food as described below.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.
- Administer **efavirenz**, Atripla, **or Symfi Lo** on an empty stomach. Avoid administration with a high-fat meal because this has the potential to increase absorption.
- **When using fixed-dose combination tablets, see other drug sections in [Appendix A: Pediatric Antiretroviral Drug Information](#) for special instructions and additional information**

Children Aged  $\geq 3$  Years and Weighing  $\geq 10$  kg:

### Once-Daily Doses of Efavirenz by Weight

Weight	Efavirenz 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
$\geq 40$ 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 into an age-appropriate food (see Special Instructions).

<sup>b</sup> Some experts recommend a dose of efavirenz 367 mg/m<sup>2</sup> body surface area (maximum dose 600 mg) because of concern for underdosing at the upper end of each weight band (see Pediatric Use in text below for details). Weight bands approximate a dose of efavirenz 367 mg/m<sup>2</sup>, with a maximum dose of 600 mg.

Adolescent (Weighing  $\geq 40$  kg) and Adult Dose:

- Efavirenz 600 mg once daily

#### [Atripla] Efavirenz plus Emtricitabine plus TDF

- Atripla should not be used in pediatric patients <40 kg as the dose of efavirenz 600 mg would be excessive.

Adult Dose:

- One tablet once daily

#### [Symfi Lo] Efavirenz plus Lamivudine plus TDF: Pediatric (Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily

**Note:** The new fixed-dose combination (Symfi Lo), which has a lower dose of efavirenz, has not yet been discussed by the Panel. The Panel will address its use in children in a later update.

about the individual drug components.

- The Food and Drug Administration cautions that efavirenz should not be used during the first trimester of pregnancy because of potential teratogenicity. However, after a review of updated evidence regarding teratogenicity risks, the [Perinatal Guidelines](#) do not restrict use of efavirenz in female adolescents and adults who are pregnant or may become pregnant.

#### Instructions for Use of Efavirenz Capsule as a Sprinkle Preparation with Food or Formula:

- Hold capsule horizontally over a small container and carefully twist to open to avoid spillage.
- Gently mix capsule contents with 1–2 teaspoons of an age-appropriate soft food (e.g., applesauce, grape jelly, yogurt) or reconstituted infant formula at room temperature.
- Administer infant formula mixture using a 10-mL syringe.
- After administration, an additional 2 teaspoons of food or infant formula must be added to the container, stirred, and dispensed to the patient.
- Administer within 30 minutes of mixing and do not consume additional food or formula for 2 hours after administration.

#### Metabolism/Elimination

- Cytochrome P450 3A (CYP3A) and CYP2B6 inducer *in vivo* and CYP2C9, 2C19, and 3A4 isozyme inhibitor *in vitro*.
- Efavirenz is not recommended for patients with moderate or severe hepatic impairment.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450, with slower metabolizers at higher risk of toxicity (see [Therapeutic Drug Monitoring](#) in the text below for information about the management of mild or moderate toxicity).

#### Atripla and Symfi Lo Dosing in Adults with Renal Impairment:

- Because these are fixed-dose combination products and TDF and emtricitabine require dose adjustment based on renal function, Atripla and Symfi Lo should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.

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

- **Metabolism:** Co-administration of efavirenz with drugs primarily metabolized by cytochrome P (CYP) 2C9, CYP2C19, CYP2B6, or CYP3A isozymes may result in altered plasma concentrations of the co-administered drugs. Drugs that induce CYP3A and CYP2B6 activity would be expected to increase the clearance of efavirenz, resulting in lower plasma concentrations. There is potential for multiple drug interactions with efavirenz. Importantly, dose adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, lopinavir/ritonavir (LPV/r), or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.
- Corrected QT (QTc) prolongation has been observed with the use of efavirenz.<sup>1,2</sup> Consider using an alternative to efavirenz in patients 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 primarily been reported in adults.
- **Rare:** QTc prolongation has been observed with the use of efavirenz.<sup>1,2</sup> A case report associated efavirenz use with marked QT prolongation and Torsades de Pointes.<sup>3</sup> An association between efavirenz and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.
- **Potential risk of teratogenicity:** For discussion, see Pediatric Use section below; see also [Efavirenz in the Perinatal Guidelines](#).

## **Resistance**

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

## **Pediatric Use**

### *Approval*

Efavirenz is Food and Drug Administration (FDA)-approved for use as part of antiretroviral therapy in children aged  $\geq 3$  months and weighing  $\geq 3.5$  kg. **Although the FDA has approved the use of Symfi Lo, the fixed-dose combination of efavirenz 400 mg plus lamivudine 300 mg plus tenofovir disoproxil fumarate (TDF) 300 mg, in children weighing  $\geq 35$  kg, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) has not yet discussed pediatric use of this new formulation and the implications of using a fixed-dose combination that contains a lower dose of efavirenz in children.**

### *Efficacy in Clinical Trials*

In clinical trials in adults and children with HIV, efavirenz used in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response.

- Efavirenz-based regimens have proven virologically superior or noninferior to a variety of regimens in adults, including those containing LPV/r, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.<sup>4-10</sup>
- Efavirenz proved inferior to dolutegravir in the SINGLE trial in adults, which compared the virologic

response of dolutegravir plus abacavir/lamivudine to the virologic response of efavirenz/TDF/emtricitabine at Weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.<sup>11</sup>

- Efavirenz used in combination with two NRTIs or with an NRTI and a protease inhibitor has been studied in children and has shown virologic potency and safety that is comparable to what has been seen in adults.<sup>12-18</sup>
- The 96-week results of the Encore 1 trial, a randomized trial in adults, showed that efavirenz 400 mg used in combination with TDF and emtricitabine was noninferior to efavirenz 600 mg used in combination with TDF and emtricitabine.<sup>19</sup>

#### *Pharmacokinetics: Pharmacogenomics*

Genetic polymorphisms in genes coding for enzymes involved in the metabolism of efavirenz may alter enzyme activity, which causes a high degree of interpatient variability in drug exposure. CYP2B6 is the primary enzyme for efavirenz metabolism, and pediatric patients with the CYP2B6-516-T/T genotype (which has an allele frequency of 20% in African Americans) have reduced metabolism, resulting in higher efavirenz levels in these patients than in those with the G/G or G/T genotype.<sup>20-24</sup> IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/kg of efavirenz using opened capsules resulted in therapeutic efavirenz concentrations in 58% of children aged <3 years with G/G or G/T genotype but excessive exposure in those with T/T genotype.<sup>25</sup> Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see discussion below).<sup>24,25</sup> Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.<sup>24,26-30</sup> The CYP2B6 T983C mutation has also been associated with reduced efavirenz clearance in African children.<sup>24</sup>

#### *Pharmacokinetics and Dosing: Infants and Children Aged <3 Years*

The Panel does not recommend use of efavirenz in children aged 3 months to <3 years. Limited pharmacokinetic (PK) data in children aged <3 years or weighing <13 kg have shown that it is difficult to achieve target trough concentrations in this age group.<sup>22,31</sup> These data show age-related differences in absorption and impact of formulation on efavirenz PKs.<sup>23</sup> Also, hepatic enzyme activity is known to change with age. Using a pharmacometric model, the increase in oral clearance of efavirenz as a function of age is predicted to reach 90% of mature value by age 9 months.<sup>23</sup> This maturation of oral clearance is postulated to result from an increase in the expression of CYP2B6 with age.<sup>23</sup> CYP2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP2B6 when compared with the CYP2B6-516-G/T or -T/T genotype.<sup>20</sup> In children with CYP2B6-516-G/G genotype, the oral clearance rate of efavirenz has been shown to be higher in children aged <5 years than in older children.<sup>20</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 HIV/tuberculosis coinfection, using efavirenz dosed by weight band based on CYP2B6 GG/GT versus T/T genotype (see Tables A1 and A2 below). When used without regard to genotype, doses higher than the FDA-approved doses resulted in therapeutic efavirenz concentrations in an increased proportion of study participants with G/G or G/T genotypes but excessive exposure in a high proportion of those with T/T genotypes.<sup>25</sup> Therefore, dosing tables have been modified so that infants and young children with T/T genotype will receive a reduced dose. Additional analyses are needed to confirm that this dose is appropriate for this subset of patients. The modified doses listed in Tables A1 and A2 are under investigation.

**Table A1. Protocol P1070 Dosing for Patients with CYP2B6-516-G/G and -G/T Genotypes (Extensive Metabolizers [EM])<sup>a</sup>**

Weight	Efavirenz Dose
5 kg to <7 kg	300 mg
7 kg to <14 kg	400 mg
14 kg to <17 kg	500 mg
≥17 kg	600 mg

**Table A2. Protocol P1070 Dosing for Patients with CYP2B6-516-T/T Genotype (Slow Metabolizers [SM])<sup>a</sup>**

Weight	Efavirenz Dose
5 kg to <7 kg	50 mg
7 kg to <14 kg	100 mg
14 kg to <17 kg	150 mg
≥17 kg	150 mg

<sup>a</sup> Investigational doses are based on IMPAACT study P1070.<sup>25</sup> Evaluation of CYP2B6 genotype is required. Therapeutic drug level monitoring is recommended with a trough measured 2 weeks after initiation of efavirenz and at age 3 years for possible dose adjustment.

The FDA has approved efavirenz for use in infants and children aged 3 months to <3 years at doses derived from a population PK model based on data from older subjects in PACTG 1021 and PACTG 382, and also from data collected during AI266-922, which is a study assessing the PK, safety, and efficacy of capsule sprinkles in children aged 3 months to 6 years (see Table B).

**Table B: FDA-Approved Dosing for Children Aged 3 Months to <3 Years (Without Regard to CYP2B6 Genotype)**

Weight	Efavirenz Dose
5 kg to <7.5 kg	150 mg
7.5 kg to <15 kg	200 mg
15 kg to <20 kg	250 mg

The FDA-approved doses are lower than the CYP2B6 extensive metabolizer (EM) doses and higher than the CYP2B6 slow metabolizer (SM) doses currently under study in P1070. Further studies are needed to determine if the FDA dosing can achieve therapeutic levels for the group aged 3 months to 3 years. There is concern that FDA-approved doses may result in frequent underdosing in CYP2B6 EMs. Estimates of efavirenz area under the curve (AUC) for FDA dosing using P1070 data were calculated using the following equation:

$$\text{P1070-observed AUC} \times \left( \frac{\text{FDA dose}}{\text{P1070 CYP2B6 genotype-directed study dose}} \right)$$

A high initial dose of efavirenz in the first version of the P1070 protocol was used to produce a target AUC of 35 to 180 mcg\*h/mL, a systemic exposure similar to that shown to be safe and effective in older children and adults.<sup>25</sup> The P1070 dosing for children aged 3 to 36 months leads to higher levels than seen with FDA recommendations for adults receiving 600 mg daily. However, the higher doses reduced the frequency of low AUCs (<35 mcg\*h/mL) with P1070 EM dosing (11% P1070 EM dosing vs. an estimated 32% with FDA dosing). The lower P1070 dose for SM genotype is predicted to reduce the frequency of high AUCs from 56% to 11% compared to the FDA genotypic agnostic dose (a dose given without consideration of genotype) in this population.

The Panel **does not recommend** use of efavirenz in children aged 3 months to <3 years. If the clinical situation demands use of efavirenz, the Panel recommends determining CYP2B6 genotype prior to use.

(See a [list of laboratories performing this testing](#).) Patients should be classified as extensive CYP2B6-516-G/G and -G/T genotype metabolizers (EMs) or slow CYP2B6-516-T/T genotype metabolizers (SMs) to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Tables A1 and A2). Whether the doses used are investigational or FDA-approved, measuring efavirenz plasma concentrations should be considered 2 weeks after initiation (see [Therapeutic Drug Monitoring](#) below). **The mid-dose efavirenz plasma concentration target of 1.0 to 4.0 mg/L derived from adult clinical monitoring data is typically also applied to trough concentrations. A study of 128 African children (aged 1.7–13.5 years) suggests that the  $C_{24h}$  threshold for increased risk of unsuppressed viral load is  $C_{24h}$  0.65 mg/L.**<sup>32</sup> Consultation with an expert is recommended before adjusting dose. In addition, when following the P1070 investigational dose recommendations, some experts would measure efavirenz concentrations at age 3 years before making the transition to the new dose.

#### *Pharmacokinetics: Children Aged $\geq 3$ Years and Adolescents*

Even with the use of FDA-approved pediatric dosing in children aged  $\geq 3$  years, efavirenz concentrations can be suboptimal.<sup>20,33-37</sup> Therefore, some experts recommend therapeutic drug monitoring (TDM) with efavirenz and possible use of higher doses in young children, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient. In one study in which the efavirenz dose was adjusted in response to measurement of the AUC, the median administered dose was efavirenz 13 mg/kg (367 mg/m<sup>2</sup>) and the range was from 3 to 23 mg/kg (69–559 mg/m<sup>2</sup>).<sup>38</sup> A PK study in 20 children aged 10 to 16 years treated with LPV/r 300 mg/m<sup>2</sup> twice daily plus efavirenz 350 mg/m<sup>2</sup> once daily showed adequacy of the lopinavir trough values but suggested that the efavirenz trough values were lower than PK targets. The authors therefore recommended that higher doses of efavirenz might be needed when these drugs are used together.<sup>39</sup>

#### *Toxicity: Children versus Adults*

The toxicity profile for efavirenz differs for adults and children. One adverse effect (AE) commonly seen in children is rash, which was reported in up to 40% of children and 27% of adults.<sup>40</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>41</sup> These symptoms usually occur early in treatment and rarely require drug discontinuation, but they can sometimes occur or persist for months. Bedtime efavirenz dosing appears to decrease the occurrence and severity of these neuropsychiatric side effects. For patients who can swallow capsules or tablets, ensuring that efavirenz is taken on an empty stomach also reduces the occurrence of neuropsychiatric AEs. The ENCORE1 study in adults demonstrated that a dose of efavirenz 400 mg is associated with fewer AEs and a noninferior virologic response when compared with the recommended 600-mg dose of efavirenz in adults.<sup>19,42</sup>

An association between efavirenz and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in a retrospective analysis of four comparative trials in adults and in the START Trial, a prospective analysis of adults.<sup>43,44</sup> This association, however, was not found in analyses of two large observational cohorts<sup>45,46</sup> and no cases of suicide were reported in a systematic review of randomized trials.<sup>41</sup> In several studies, the incidence of neuropsychiatric AEs was correlated with efavirenz plasma concentrations, and the symptoms occurred more frequently in patients with higher concentrations.<sup>47-51</sup> In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously. Adverse CNS events occurred in 14% of children receiving efavirenz in clinical studies<sup>52</sup> and in 30% of children with efavirenz concentrations  $>4$  mcg/mL.<sup>21</sup> CNS AEs may be harder to detect in children because it is difficult to assess neurologic symptoms such as impaired concentration, sleep disturbances, or behavior disorders in these patients.

#### *Toxicity: QTc Prolongation*

CYP2B6 genetic variants are known to slow efavirenz clearance. The CYP2B6\*6 allele is associated



with reduced clearance and increased efavirenz-induced CNS toxicity, hepatic injury, and treatment discontinuation.<sup>47,48</sup> Homozygous carriers of the CYP2B6\*6 allele (CYP2B6\*6/\*6) may be at increased risk for efavirenz-induced rate QTc prolongation. The CYP2B6\*6 allele codes for the CYP2B6-516-G>T complementary DNA nucleotide change;<sup>53</sup> therefore, CYP2B6\*6/\*6 carriers can be categorized as SMs. The effect of efavirenz on the QTc interval was evaluated in a study of 58 healthy adult subjects enriched for CYP2B6 polymorphisms. A positive relationship between efavirenz concentration and QTc prolongation was observed. The mean QTc prolongation and its upper-bound 90% confidence interval are 8.7 ms and 11.3 ms in subjects with CYP2B6\*6/\*6 genotype following the administration of efavirenz 600 mg daily for 14 days.<sup>1</sup> Drugs that prolong the mean QTc interval by more than 20 ms have a substantially increased likelihood of being pro-arrhythmic. While the data on drugs that prolong the mean QTc interval by more than 5 ms but less than 20 ms are inconclusive, some of these drugs have been associated with pro-arrhythmic risk.<sup>54</sup> Consider using an alternative to efavirenz in patients 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>

### *Toxicity: Potential Risk of Teratogenicity*

In prior versions of the Perinatal Guidelines, efavirenz use was not recommended before 8 weeks' gestational age because of concerns regarding potential teratogenicity. Although this caution is still included in the package insert, and efavirenz use has been associated with significant teratogenic effects in nonhuman primates, results of a large meta-analysis have been reassuring that risks of neural tube defects after first-trimester efavirenz exposure are not greater than those seen in the general population.<sup>2,55</sup> As a result, the current Perinatal Guidelines do not include the restriction of use before 8 weeks' gestation, consistent with both the British HIV Association and World Health Organization guidelines for use of antiretroviral drugs during pregnancy (both of which note that efavirenz can be used throughout pregnancy).<sup>56,57</sup> Importantly, women who become pregnant on suppressive efavirenz-containing regimens should continue their current regimens.

For a comprehensive discussion, see [Efavirenz](#) in Appendix B of the [Perinatal Guidelines](#).<sup>58</sup>

### *Therapeutic Drug Monitoring*

In the setting of potential toxicity, it is reasonable for a clinician to use TDM to determine whether the toxicity is due to an efavirenz concentration in excess of the normal therapeutic range.<sup>59,60</sup> Dose reduction would be considered appropriate management of drug toxicity; however, dose reduction should be used with caution. Also, TDM should be considered when dosing efavirenz in children aged 3 months to <3 years due to increased oral clearance and variable PK properties in this young age group. An efavirenz concentration, measured 2 weeks after initiation, and consultation with an expert should be considered to inform dose adjustment. In addition, some experts would measure efavirenz concentrations at age 3 years after making the transition to the new dose if dosing was initiated at age <3 years using investigational dose recommendations. The currently accepted minimum effective concentration of efavirenz is a mid-dose concentration ( $C_{12}$ ) >1 mg/L in adults, and concentrations >4.0 mg/L are associated with CNS side effects.<sup>48</sup> A recent study in children showed that a higher proportion of children with a  $C_{12}$  <1 mg/L showed evidence of viral replication than those with a  $C_{12}$  >1 mg/L.<sup>61</sup> However, the validity using a single target has been called into question.<sup>62</sup> In addition, a lower limit  $C_{12}$  >0.7 mg/L was most predictive of virologic outcome in a study of 180 adults.<sup>63</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>32</sup>

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## Etravirine (ETR, Intelence, TMC 125) (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: 25 mg, 100 mg, and 200 mg

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

#### Pediatric Dose:

- Not approved for use in children aged <6 years. Studies in infants and children aged 2 months to 6 years are under way.

#### Antiretroviral-Experienced Children and Adolescents Aged 6–18 Years and Weighing $\geq 16$ kg

Body Weight	Dose
16 kg to <20 kg	100 mg twice daily
20 kg to <25 kg	125 mg twice daily
25 kg to <30 kg	150 mg twice daily
$\geq 30$ kg	200 mg twice daily

#### Adult Dose (Antiretroviral-Experienced Patients):

- 200 mg twice daily following a meal

### Selected Adverse Events

- Nausea
- Diarrhea
- Rash, including Stevens-Johnson syndrome
- Hypersensitivity with rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

### Special Instructions

- Always administer etravirine following a meal. Area under the curve of etravirine is decreased by about 50% when the drug is taken on an empty stomach. The type of food does not affect the exposure to etravirine.
- Etravirine tablets are sensitive to moisture; store at room temperature in original container with desiccant.

#### Instructions for Dispersing Etravirine Tablets in Liquid:

- Patients who are unable to swallow etravirine tablets may disperse the tablets in liquid.
- Place the tablet(s) in 5 mL (1 teaspoon) of water, or enough liquid to cover the medication, and stir well until the water looks milky. If desired, add more water or, alternatively, orange juice or milk. **Note:** Patients should not place the tablets in orange juice or milk without first adding water. The use of grapefruit juice, warm ( $>40^{\circ}$  C) drinks, or carbonated beverages should be avoided.
- Drink immediately, then rinse the glass several times with water, orange juice, or milk and completely swallow the rinse each time to make sure the entire dose is consumed.

### Metabolism/Elimination

- Etravirine is an inducer of cytochrome P450 3A4 (CYP3A4) and an inhibitor of CYP2C9, CYP2C19, and P-glycoprotein. It is a substrate

for CYP3A4, 2C9, and 2C19.

- Etravirine is involved in multiple interactions with antiretroviral agents and other drugs (see text below).

#### Etravirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

#### Etravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required in patients with renal impairment.

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

- Etravirine is associated with multiple drug interactions. Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions with etravirine.
- Etravirine **should not be co-administered** with the following antiretroviral (ARV) drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, and unboosted protease inhibitors (PIs). It **should not be administered** with other non-nucleoside reverse transcriptase inhibitors (NNRTIs) (i.e., nevirapine, efavirenz, rilpivirine). Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir,<sup>1</sup> but no dose adjustment is currently recommended when etravirine and raltegravir are used together. Etravirine significantly reduces plasma concentrations of dolutegravir **and elvitegravir/cobicistat (EVG/c)**. Dolutegravir should only be used with etravirine when co-administered with atazanavir/ritonavir, darunavir/ritonavir (DRV/r), or lopinavir/ritonavir. **Etravirine should not be co-administered 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 etravirine. However, patients who have a history of severe rash with prior NNRTI use should not receive etravirine.
- *Less common (more severe):* Peripheral neuropathy, severe rash, hypersensitivity reactions (HSRs), and erythema multiforme have all been reported. Instances of severe rash have included Stevens Johnson syndrome, and HSRs have included constitutional findings and organ dysfunction, including hepatic failure. Discontinue etravirine immediately if signs or symptoms of severe skin reactions or HSRs develop (including severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, and eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping etravirine treatment after the onset of severe rash may result in a life-threatening reaction. It is recommended that patients who have a prior history of severe rash with nevirapine or efavirenz not receive etravirine.

### **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

Etravirine is Food and Drug Administration-approved for use in ARV-experienced children and adolescents aged 6 years to 18 years.

### Efficacy in Clinical Trials

In the PIANO study,<sup>2</sup> ARV-experienced children aged 6 years to <18 years received etravirine with a ritonavir-boosted PI as part of an optimized background regimen. At Week 24, 67% of these participants had plasma HIV RNA concentrations <400 copies/mL and 52% had <50 copies/mL. At Week 48, 56% of the participants had <50 copies/mL and a mean increase in their CD4 T lymphocyte cell counts of 156 cells/mm<sup>3</sup> from baseline. A greater fraction of children aged 6 years to <12 years had plasma HIV-1 RNA <50 copies/mL than adolescents aged 12 years to <18 years (68% vs. 48%).

In a retrospective study of 23 adolescents and young adults, 78% of participants achieved an HIV-1 RNA <50 copies/mL at a median of 48.4 weeks of follow-up.<sup>3</sup>

### Pharmacokinetics

In a Phase 1 dose-finding study involving children aged 6 years to 17 years, 17 children were given etravirine 4 mg/kg twice daily. Two pharmacokinetic (PK) parameters—area under the curve for 12 hours post-dose ( $AUC_{0-12h}$ ) and minimum plasma concentration ( $C_{min}$ )—were below preset statistical targets based on prior studies involving adults.<sup>4</sup> On the basis of acceptable PK parameters, the higher dose (etravirine 5.2 mg/kg twice daily; maximum 200 mg per dose) was chosen for evaluation in the Phase 2 PIANO study. Exposures (mean  $AUC_{0-12h}$ ) remained lower in older adolescents than in adults and younger children, and exposures were lower in Asian participants than in either white or black participants. In the PIANO study children and adolescents with etravirine concentrations in the lowest quartile (<2,704 ng\*h/mL or  $C_{0h}$  <145 ng/mL) were less likely to achieve sustained virologic responses (plasma viral load <50 copies/mL) after 48 weeks of treatment than those with etravirine concentrations in the upper three quartiles.<sup>5</sup>

	Mean $AUC_{0-12h}$ (ng*h/mL)	Mean $C_{0h}$ (ng/mL)
Children Aged 6–11 Years (N = 41)	5,684	377
Adolescents Aged 12–17 Years (N = 60)	4,895	325
Adults	5,506	393

**Key to Acronyms:**  $AUC_{0-12h}$  = Area under the curve for 12 hours post-dose;  $C_{0h}$  = pre-dose concentration during chronic administration

Etravirine is often combined with DRV/r for treatment of adults with HIV with prior virologic failure. Cressey et al. examined PK data from 36 adolescents and young adults receiving etravirine 200 mg twice daily in combination with DRV/r 600 mg/100 mg twice daily. The PK exposures of both agents were similar to those seen in adults, although with high interindividual variability.<sup>6</sup> The PKs of both drugs were also studied in adolescents and young adults receiving DRV/r 800 mg/100 mg once daily with either etravirine 200 mg twice daily or etravirine 400 mg once daily.<sup>7</sup> Darunavir concentrations were higher when co-administered with etravirine, particularly when the latter was given in doses of 200 mg twice daily. Etravirine exposures were lower when given with DRV/r, particularly when etravirine was given twice daily, although the authors commented on the limited sample size involved in these studies. While the combination of etravirine and DRV/r has been effective in a small cohort of adolescents with HIV<sup>8</sup> and in 51% of participants in the PIANO study,<sup>2,5</sup> these data suggest a need for additional study of PK interactions involving etravirine and other ARV agents in pediatric patients, including regimens that do not include ritonavir-boosted PIs. Until such data become available, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends using etravirine as part of a regimen that includes a ritonavir-boosted PI.



## Toxicity

In the PIANO study, rash and diarrhea were the most common adverse drug reactions deemed possibly related to etravirine. Rash (Grade 2 or higher) occurred in 13% of pediatric subjects and emerged at a median of 10 days, lasting a median of 7 days. Rash was observed more frequently in females (17 of 64; 26.6%) than in males (6 of 37; 16.2%). Etravirine was discontinued due to rash in four individuals (4% of all participants), all of whom were female. Diarrhea occurred in three individuals (3% of participants) and was only reported in adolescents.

## References

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## Nevirapine (NVP, Viramune) (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:** Immediate-release 200 mg, extended-release (XR) 100 mg and 400 mg

**Suspension:** 10 mg/mL

### Generic Formulations

**Tablets:** Immediate-release 200 mg, extended-release (XR) 400 mg only

**Suspension:** Generic suspension is no longer available in the United States.

**Note:** While the suspension formulation of brand name nevirapine (Viramune) is available, it is not typically stocked in local pharmacies or hospitals. Have the pharmacy ask their drug wholesaler to order directly from the Boehringer-Ingelheim distribution center. The distribution center should be able to ship the formulation directly to the pharmacy.

### Dosing Recommendations

#### Neonate and Infant (Aged $\leq 14$ Days) Dose for Prevention:

- See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#).

#### Pediatric Dose for Treatment of HIV

**Note:** In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of the enzymes involved in its metabolism. This may not be necessary in children aged  $< 2$  years (see footnote<sup>a</sup> and text below).

#### Immediate Release Tablets and Suspension Formulations

*Aged  $< 1$  Month (This **Investigational Dose** is Not Food and Drug Administration-Approved):*

- 34–37 weeks gestational age: Nevirapine 4 mg/kg/dose twice daily for the first week, increasing to nevirapine 6 mg/kg/dose twice daily thereafter (no lead in; please see text and footnote<sup>a</sup>)
- $\geq 37$  weeks gestational age to age  $< 1$  month: Nevirapine 6 mg/kg/dose twice daily (no lead in; please see text and footnote<sup>a</sup>)
- See the Special Considerations for Dosing: Neonates and Premature Infants section below.

*Aged  $\geq 1$  Month to  $< 8$  Years:*

- 200 mg/m<sup>2</sup> of body surface area (BSA)/dose twice daily after lead-in dosing.<sup>a</sup> In children aged  $\leq 2$  years, some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 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 suspension well before administering and store at room temperature.
- Can be given without regard to food.
- Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14 day lead-in period, do not increase dose until rash resolves (see the Major Toxicities section below).
- Nevirapine extended-release tablets **must** be swallowed whole. They cannot be crushed, chewed, or divided.
- If nevirapine dosing is interrupted for more than 14 days, nevirapine should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see the Dosing Considerations: Lead-In Requirement section below).
- Most cases of nevirapine-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see the Major Toxicities section below).

### Aged ≥8 Years:

- 120–150 mg/m<sup>2</sup> BSA/dose twice daily after lead-in dosing<sup>a</sup> (maximum dose of immediate-release tablets is nevirapine 200 mg twice daily)
- When adjusting the dose for a growing child, the mg dose need not be decreased as the child reaches age 8 years; rather, the mg dose is left static to achieve the appropriate mg-per-m<sup>2</sup> dose as the child grows, as long as there are no untoward effects.

BSA Range	NVP XR
0.58 m <sup>2</sup> to 0.83 m <sup>2</sup>	200 mg once daily (2 x 100 mg)
0.84 m <sup>2</sup> to 1.16 m <sup>2</sup>	300 mg once daily (3 x 100 mg)
≥1.17 m <sup>2</sup>	400 mg once daily (1 x 400 mg)

**Key to Abbreviations:** BSA = body surface area; NVP XR = nevirapine extended release

### Extended-Release Formulation

#### Aged ≥6 Years:

- Patients aged ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing.<sup>a</sup>

#### Adolescent and Adult Dose: <sup>a,b</sup>

- 200 mg twice daily or 400 mg extended release once daily **after lead-in dosing**.

### Nevirapine Used in Combination with Lopinavir/Ritonavir:

- A higher dose of lopinavir/ritonavir may be needed (see [Lopinavir/Ritonavir](#)).

- Nevirapine **should not be co-administered to patients receiving atazanavir (with or without ritonavir)**.

- Nevirapine **increases the metabolism of lopinavir. A dose adjustment of lopinavir is recommended (see [Lopinavir/Ritonavir](#))**.

### Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% of nevirapine dose is excreted in urine (glucuronidated metabolites).

#### Nevirapine Dosing in Patients with Renal Failure Who Are Receiving Hemodialysis:

- An additional dose of nevirapine should be given following dialysis.

#### Nevirapine Dosing in Patients with Hepatic Impairment:

- Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

<sup>a</sup> Nevirapine is usually initiated at a lower dose and increased in a stepwise fashion to allow for induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The stepwise increase in dose decreases the occurrence of rash. Clinicians should initiate therapy with the age-appropriate dose of the immediate-release formulation once daily (half-daily dose) for the first 14 days of therapy. If there is no rash or untoward effect, at 14 days of therapy, increase to the age-appropriate full dose, administered twice daily, of the immediate-release preparation. However, in children aged ≤2 years, some experts initiate nevirapine without a lead-in (see Dosing Considerations: Lead-In Requirement and Special Considerations for Dosing: Neonates and Premature Infants sections below). In patients who are already receiving full-dose, immediate-release nevirapine, extended-release tablets can be used without the 200-mg lead-in period. Patients must swallow nevirapine extended-release tablets whole. They must not be chewed, crushed, or divided. Patients must **never** take more than 1 form of nevirapine at the same time. Dose should not exceed 400 mg daily.

<sup>b</sup> Symptomatic hepatitis, including fatal hepatic necrosis, occurs at a significantly higher frequency in antiretroviral (ARV)-naive women with pre-nevirapine CD4 T lymphocyte (CD4) cell counts >250 cells/mm<sup>3</sup> and in ARV-naive men with pre-nevirapine CD4 counts >400 cells/mm<sup>3</sup>. Nevirapine **should not be initiated** in these patients unless the benefit clearly outweighs the risk.

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

- **Metabolism:** Induces hepatic cytochrome P450, including 3A (CYP3A) and 2B6; autoinduction of metabolism occurs in 2 to 4 weeks, with a 1.5- to two-fold increase in nevirapine clearance. There is potential for multiple drug interactions. Some genetic polymorphisms of CYP2B6 can increase in nevirapine serum concentration by affecting drug metabolism in a similar manner—but to a lesser extent—than the changes observed with efavirenz. Altered adverse effect profiles related to elevated

nevirapine levels have not been documented, probably because there are alternative CYP metabolic pathways for nevirapine;<sup>1</sup> however, CYP2B6 polymorphisms can vary greatly among populations, which may account for differences in drug exposure. Please see [Efavirenz](#) section for further details.

- Before nevirapine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

### **Major Toxicities**

**Note:** These toxicities are seen with continuous dosing regimens, not during single-dose nevirapine prophylaxis.

- *More common:* Skin rash (some severe cases have required hospitalization, and some cases have been life-threatening, including instances of Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be discontinued and not restarted in children or adults who develop severe rash, rash with constitutional symptoms (i.e., fever, oral lesions, conjunctivitis, or blistering), or rash with elevated hepatic transaminases. Nevirapine-associated skin rash usually occurs within the first 6 weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase the dose until rash resolves. However, the risk of developing nevirapine resistance with extended lead-in dosing is unknown and is a concern that 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 in the first 12 weeks of therapy and may be associated with rash or other signs or symptoms of hypersensitivity reaction. Risk factors for nevirapine-related hepatic toxicity in adults include baseline elevation in serum transaminase levels, hepatitis B or hepatitis C virus infection, female gender, and higher CD4 T lymphocyte (CD4) cell count at time of therapy initiation (CD4 cell count >250 cells/mm<sup>3</sup> in adult females and >400 cells/mm<sup>3</sup> in adult males). In children, there is a three-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage >15%.<sup>2</sup> Hypersensitivity reactions have been reported, including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise, and significant hepatic abnormalities. Nevirapine **should be discontinued and not restarted** in children or adults who develop symptomatic hepatitis, severe transaminase elevations, or hypersensitivity reactions.

### **Resistance**

The International 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*

Nevirapine is Food and Drug Administration (FDA)-approved for treatment of HIV in children from infancy (aged ≥15 days) onward and remains a mainstay of therapy, especially in resource-limited settings.<sup>3-11</sup> The extended-release tablet formulation has been FDA-approved for use in children aged ≥6 years.

#### *Efficacy in Clinical Trials*

Randomized clinical trials in children have demonstrated that lopinavir/ritonavir (LPV/r) is superior to nevirapine in young children but not in older children. P1060 demonstrated the superiority of LPV/r over nevirapine in children aged <3 years, as have observational studies. PENPACT-1 and PROMOTE-pediatrics enrolled older children receiving nevirapine or efavirenz and showed no differences between a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen and protease inhibitor (PI)-based regimen.<sup>12-18</sup>

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission,

nevirapine-based antiretroviral therapy (ART) is less likely to control viral load than LPV/r-based ART. In P1060, a large randomized clinical trial, 153 children with HIV and previous exposure to nevirapine for perinatal prophylaxis (mean age 0.7 years) were randomly assigned to treatment with zidovudine and lamivudine plus either nevirapine or LPV/r. At 24 weeks post-randomization, 24% of children in the zidovudine/lamivudine/nevirapine arm reached a virologic endpoint (virologic failure defined as  $<1$  log decrease in HIV RNA in Weeks 12 to 24 or HIV RNA  $>400$  copies/mL at Week 24) compared with 7% of children in the zidovudine/lamivudine/lopinavir/ritonavir arm ( $P = 0.0009$ ). When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the PI arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% of children in the LPV/r arm ( $P = 0.027$ ).<sup>15</sup> Similar results were reported in a comparison study of nevirapine and LPV/r in children aged 6 to 36 months **not** previously exposed to nevirapine, suggesting that LPV/r-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.<sup>12</sup>

Extended-release nevirapine (400-mg tablets) was 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 nevirapine and had plasma HIV RNA  $<50$  copies per mL prior to enrollment. Participants were stratified according to age (aged 3 years to  $<6$  years, 6 years to  $<12$  years, and 12 years to  $<18$  years). Following an 11-week period with immediate-release nevirapine, participants were treated with nevirapine extended-release tablets once daily in combination with other antiretroviral (ARV) drugs for 10 days, after which steady-state pharmacokinetics (PK) were determined.<sup>19</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 nevirapine extended release through a minimum of 24 weeks of treatment. Of the 40 participants who entered the treatment extension phase, 39 completed at least 24 weeks of treatment. After 24 weeks or more of treatment with nevirapine extended release, all 39 participants continued to have plasma HIV RNA  $<50$  copies per mL.<sup>20</sup>

### ***General Dosing Considerations***

Body surface area (BSA) has traditionally been used to guide nevirapine dosing in infants and young children. It is important to avoid under-dosing of nevirapine because a single point mutation (K103N) in the HIV genome may confer NNRTI resistance to both nevirapine and efavirenz. Younger children (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 nevirapine than older children.<sup>8,9</sup> Because of this, it is recommended that dosing for children aged  $<8$  years be nevirapine 200 mg/m<sup>2</sup> of BSA per dose when given twice daily (maximum dose of the immediate-release preparation is 200 mg twice daily) or nevirapine 400 mg/m<sup>2</sup> of BSA per dose when administered once daily as the extended-release preparation (maximum dose of the extended-release preparation is nevirapine 400 mg/dose once daily). For children aged  $\geq 8$  years, the recommended dose of the immediate-release preparation is nevirapine 120 mg/m<sup>2</sup> of BSA per dose (with a maximum dose of nevirapine 200 mg) administered twice daily. The maximum dose of the extended-release preparation is nevirapine 400 mg once daily for children aged  $\geq 6$  years. When adjusting the dose in a growing child, the milligram dose need not be decreased (from nevirapine 200 mg/m<sup>2</sup> to 120 mg/m<sup>2</sup>) as the child reaches 8 years; rather, the milligram dose is left static if there are no untoward effects, and the dose is allowed to achieve the appropriate mg/m<sup>2</sup> dose as the child grows. Some practitioners dose nevirapine at 150 mg/m<sup>2</sup> of BSA every 12 hours or nevirapine 300 mg/m<sup>2</sup> per dose once daily if using the extended-release preparation (with a maximum of nevirapine 200 mg per dose twice daily for the immediate-release tablets or nevirapine 400 mg per dose once daily for the extended-release tablets) regardless of age, as recommended in the FDA-approved product label.

### ***Dosing Considerations: Lead-In Requirement***

One explanation for the poorer performance of nevirapine in the P1060 trial was the potential for under-dosing during the lead-in period. This potential for under-dosing with an increased risk of resistance has led to re-evaluation of lead-in dosing in children who are naive to nevirapine therapy. Traditional dosing of

nevirapine is initiated with an age-appropriate dose once daily (nevirapine 200 mg/m<sup>2</sup> in infants aged ≥15 days and children aged <8 years using the immediate-release preparations) during the first 2 weeks of treatment to allow for the autoinduction of the liver enzymes CYP3A and CYP2B6, which are involved in nevirapine metabolism.

Studies have previously indicated that there is a potential for greater drug toxicity without lead-in dosing; however, most of these studies have been performed in adult cohorts.<sup>21</sup> The CHAPAS-1 Trial<sup>22</sup> randomized 211 children to initiate ART with immediate-release nevirapine without a lead-in (age-appropriate dose given twice daily) or with a lead-in (age-appropriate dose given once daily) for 2 weeks followed by standard twice-daily dosing of the immediate-release preparation. Children were followed for a median of 92 weeks (with a range of 68–116 weeks), and there was no difference in the frequency of Grade 3 or 4 adverse events between the two groups. The group that initiated nevirapine without a lead-in had a statistically significant increase in Grade 2 rash, but the majority of subjects were able to continue nevirapine therapy after a brief interruption. CD4 and virologic endpoints were no different through 96 weeks. After children had been on nevirapine for two weeks, investigators conducted a substudy that examined nevirapine plasma concentrations 3 to 4 hours after a morning dose of nevirapine.

For children aged <2 years, 13% (3/23) initiating at full dose versus 32% (7/22) initiating at half dose had subtherapeutic nevirapine levels (<3 mg/L) at 2 weeks ( $P = 0.16$ ). There were no rash events in the substudy group of participants aged <2 years; in the parent CHAPAS study, there was a strong age effect on rash occurrence, with the risk of rash increasing with increasing age). These findings suggest that a lead-in dose may not be necessary in young patients.<sup>23</sup>

A re-appraisal of nevirapine dosing has been advocated in older children. Gopalan et al. analyzed nevirapine concentrations in 20 children, median age 9 years, who were just starting a nevirapine-based ART regimen. Subtherapeutic nevirapine concentrations, which were defined as concentrations ≤4 mcg/mL, occurred more frequently among children aged ≤8 years ( $n = 8$ ) than among children aged >8 years ( $n = 12$ ). Half of the children experienced virologic failure by Week 48.<sup>24</sup> Gopalan et al. suggested that rapid metabolism of nevirapine by CYP2B6 in this particular population may have confounded the results. The small number of participants in this study make the findings difficult to interpret, but the authors recommended a thorough review of nevirapine dose escalation strategies in children. Reinitiating half-dose nevirapine for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes,<sup>25</sup> and the results of CHAPAS-1, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends restarting full-dose nevirapine in children who interrupt therapy for 14 days or less.

### ***Special Considerations for Dosing: Neonates and Premature Infants***

For neonates and premature infants (which includes infants up to 42 weeks, corrected gestational age), PK data are currently inadequate to formulate an effective complete ART regimen. Although dosing is available for zidovudine and lamivudine, data are inadequate for other classes of ART. On the basis of PK modeling, an investigational dose of nevirapine 6 mg/kg administered twice daily has been proposed for full-term infants who receive HIV diagnoses in the first few days of life.<sup>26–30</sup> However, a dose of nevirapine 4 mg/kg/dose twice daily has been chosen for the first week of life in infants born between 34 and 37 weeks' gestation, followed by a nevirapine 6 mg/kg/dose administered twice daily thereafter. Dose adjustments may be required if a premature infant has documented HIV infection in the first week of life. PK of nevirapine using 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 PK to maintain trough concentrations of nevirapine greater than 3 mcg/mL in the majority of infants.<sup>31</sup> Providers considering treatment of infants aged <2 weeks or premature infants should contact a pediatric HIV expert for guidance, because the decision about whether to treat an infant and what drugs to use will involve weighing the risks and benefits of using unapproved ART dosing and incorporating case-specific factors, such as exposure to ARV prophylaxis.

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## Rilpivirine (RPV, Edurant) (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

**Tablet:** 25 mg

#### Fixed-Dose Combination Tablet:

- [Complera] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Odefsey] Emtricitabine 200 mg plus rilpivirine 25 mg plus tenofovir alafenamide (TAF) 25 mg
- [Juluca] Dolutegravir 50 mg plus rilpivirine 25 mg

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

#### Children Aged <12 Years:

- Not Food and Drug Administration-approved for use in children aged <12 years. For more information regarding consideration for use in children aged <12 years and weighing  $\geq 35$  kg, see the Pharmacokinetics section below.

#### Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- 25 mg once daily in antiretroviral (ARV)-naive patients who have HIV RNA  $\leq 100,000$  copies/mL or in patients who are virologically suppressed (HIV RNA <50 copies/mL) with no history of virologic failure or resistance to rilpivirine and other ARV drugs in the new regimen.

#### Combination Tablets

[Complera] Emtricitabine plus Rilpivirine plus TDF

#### Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily in treatment-naive patients with baseline viral load  $\leq 100,000$  copies/mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who are currently on their first or second regimen and who have been virologically suppressed (HIV-1 RNA <50 copies per mL) for  $\geq 6$  months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Complera.

[Odefsey] Emtricitabine plus Rilpivirine plus TAF

#### Adolescent (Weighing $\geq 35$ kg) and Adult Dose:

- One tablet once daily with a meal as initial therapy in treatment-naive patients with

### Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction/Rash with Eosinophilia and Systemic Symptoms)
- Hepatotoxicity
- Altered ACTH stimulation test of uncertain clinical significance

### Special Instructions

- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL due to increased risk of virologic failure.
- Patients must be able to take rilpivirine with a meal of at least 500 calories on a regular schedule (a protein drink alone does not constitute a meal).
- Do not use rilpivirine with other non-nucleoside reverse transcriptase inhibitors.
- Do not use rilpivirine with proton pump inhibitors.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug that has a known risk of Torsades de Pointes (for more information see [CredibleMeds](#))
- When using fixed-dose combination (FDC) tablets, see other sections of the [Drug Appendix](#) for special instructions and additional information about the individual components of the FDC.

HIV-1 RNA  $\leq$ 100,000 copies per mL. One tablet once daily can also be used to replace a stable ARV regimen in patients who have been virologically suppressed (HIV-1 RNA  $<$ 50 copies per mL) for  $\geq$ 6 months with no history of treatment failure and no known current or past substitutions associated with resistance to the individual components of Odefsey.

### **[Juluca] Dolutegravir plus 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-1 RNA  $<$ 50 copies per mL) on a stable ARV regimen for  $\geq$ 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.
- Not approved for children or adolescents. See Simplification of Treatment section below.

## **Metabolism/Elimination**

- Cytochrome P450 (CYP) 3A substrate

### Rilpivirine Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment.
- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but it does not affect glomerular filtration.

### Rilpivirine Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with mild or moderate renal impairment.
- The FDC drugs Complera and Odefsey should not be used in patients with creatinine clearance  $<$ 50 or  $<$ 30 mL/min, respectively, or in patients who require dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease, so monitoring for adverse effects is especially important in these patients.
- When using Complera, see the TDF section of the guidelines; when using Odefsey, see the TAF section.

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

- *Metabolism:* Rilpivirine is a cytochrome P (CYP) 3A substrate and requires dose adjustments when administered with CYP 3A-modulating medications.
- A patient's medication profile should be carefully reviewed for potential drug interactions before rilpivirine is administered.
- Co-administering rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.
- Antacids should only be taken at least 2 hours before or at least 4 hours after rilpivirine.
- H2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after rilpivirine.
- Do not use rilpivirine with proton pump inhibitors.
- Rifampin and rifabutin significantly reduce rilpivirine plasma concentrations; co-administration of rifampin with rilpivirine is **contraindicated**. For patients concomitantly receiving rifabutin, rilpivirine dose should be increased (doubled) to 50 mg once daily, taken with a meal.
- In a cohort of adolescent patients, rilpivirine exposure was increased two- to three-fold when administered in combination with darunavir/ritonavir (DRV/r).<sup>1</sup>

## Major Toxicities

- *More common:* Insomnia, headache, and rash.
- *Less common (more severe):* Depression or mood changes, suicidal ideation.
- In adult studies, 7.3% of patients treated with rilpivirine showed a change in adrenal function identified by an abnormal 250-microgram ACTH stimulation test (peak cortisol level <18.1 micrograms/dL). **In an adolescent study**, 6 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.

## Pediatric Use

### Approval

With the viral load and antiretroviral (ARV) resistance restrictions noted above, rilpivirine (**Edurant**) used in combination with other antiretroviral agents,<sup>2</sup> the combination tablet rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera),<sup>3</sup> and the combination tablet rilpivirine/emtricitabine/tenofovir alafenamide (Odefsey) are all Food and Drug Administration (FDA)-approved for use in persons aged  $\geq 12$  years and weighing  $\geq 35$  kg.<sup>4</sup> **The combination tablet of dolutegravir/rilpivirine (Juluca) is not approved for use in pediatric or adolescent patients at the time of this review.**<sup>5</sup>

### Efficacy in Clinical Trials

A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be non-inferior to efavirenz. Subjects with pretreatment HIV viral loads  $\geq 100,000$  copies/mL who received rilpivirine had higher rates of virologic failure than those who received efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral load  $\leq 100,000$  copies/mL.<sup>6-9</sup>

A study of treatment-naïve adolescents aged 12 to 18 years demonstrated that rilpivirine 25 mg, given once daily in combination with two nucleoside reverse transcriptase inhibitors (NRTIs), was well tolerated over 48 weeks. Among adolescents with baseline viral loads  $\leq 100,000$  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 selected for rilpivirine use need to be able to take the drug on a regular schedule and with a full meal, which may limit its usefulness for some adolescents with irregular schedules. The FDC formulation, Odefsey, is a small pill and can be useful for select patients who might want to switch from a multi-pill regimen and who do not have any drug resistance mutations **to the components of Odefsey**.

**A Spanish multicenter observational study enrolled 17 adolescents (aged <18 years of age) who acquired HIV perinatally to receive emtricitabine/tenofovir disoproxil fumarate/rilpivirine (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 a non-nucleoside reverse transcriptase inhibitor-based regimen, and one had not received antiretroviral therapy (ART). After a median follow-up of 90 weeks (for participants with undetectable viral loads at baseline) or 40 weeks (for participants with detectable viral loads at baseline), 86% and 89% of patients, respectively, achieved and maintained an undetectable viral load. None of the patients discontinued rilpivirine-based therapy because of adverse effects; no skin rashes or central nervous system (CNS)-related events were observed. In addition, serum lipids improved and two adolescents with a history of insomnia and abnormal dreams while receiving efavirenz-based therapy did not report similar problems while receiving rilpivirine-based therapy.**<sup>11</sup>

## Pharmacokinetics

The pharmacokinetics (PK), safety, and efficacy of rilpivirine in children aged <12 years have not been established but are under study in patients aged 6 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 decided that that rilpivirine may be appropriate in select children aged <12 years and weighing  $\geq 35$  kg. However, the Panel advises consulting an expert in pediatric HIV infection prior to use in this age group.

An international (India, Thailand, Uganda, and South Africa) Phase 2 trial, PAINT TMC278, investigated a 25-mg dose of rilpivirine given in combination with two NRTIs in ARV-naive adolescents aged 12 to <18 years, weighing  $\geq 32$  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 to  $\leq 15$  years and 12 youth aged >15 to  $\leq 18$  years underwent intensive PK evaluations after an observed dose of rilpivirine taken with a meal. PK were comparable to those in adults; results are listed in the table below.<sup>12</sup>

**Table A. Rilpivirine Pharmacokinetics in Adults and in Adolescents Aged 12 to <18 Years<sup>2</sup>**

Parameter	Adults	Adolescents Aged 12 to <18 years
Dose	25 mg once daily	25 mg once daily
Number of Participants Studied	679	34
<b>AUC<sub>24h</sub> (ng•h/mL)</b>		
Mean $\pm$ Standard Deviation	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 $\pm$ Standard Deviation	79 $\pm$ 35	85 $\pm$ 40
Median (Range)	73 (2–288)	79 (7–202)

**Key to Acronyms:** AUC = area under the curve; C<sub>0h</sub> = plasma concentration just prior to next dose

In a PK study of youth aged 13 to 23 years receiving rilpivirine,<sup>1</sup> rilpivirine exposure was comparable to the results from PAINT in patients receiving 25-mg doses rilpivirine without DRV/r and substantially higher in those receiving 25-mg doses rilpivirine with DRV/r (AUC = 6,740 ng•h/mL). No dose adjustments are currently recommended for adults when rilpivirine is used with DRV/r, where a similar two- to three-fold increase in rilpivirine exposure has been reported.<sup>2</sup>

Rilpivirine has been reported to have fewer CNS adverse effects and has been promoted as a replacement ARV for some patients who experience CNS effects while receiving efavirenz. However, there has been concern that prolonged efavirenz half-life might have an impact on rilpivirine levels after a drug switch. A Thai study evaluated 20 Thai adolescents 4 weeks after switching from efavirenz to rilpivirine. The PK parameters of rilpivirine in this study population were comparable with those in previous pediatric (PAINT) and adult (ECHO/THRIVE) PK substudies. No virologic failure was detected at 12 or 24 weeks and no patients discontinued rilpivirine because of adverse effects.<sup>13</sup>

## Simplification of Treatment

Dolutegravir/rilpivirine (Juluca) is a fixed-dose combination tablet that contains dolutegravir 50 mg and rilpivirine 25 mg. The recently reported results from two trials in adults (SWORD-1 and SWORD-2) support FDA approval of dolutegravir/rilpivirine as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations to dolutegravir or rilpivirine. The participants were randomized to receive dolutegravir/rilpivirine or to continue their suppressive ARV regimen. After 48 weeks of treatment, 95% of

patients in both arms maintained HIV RNA <50 copies/mL.<sup>14</sup> More adverse events (AEs) were reported and more AEs led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.<sup>15</sup> Although dolutegravir/rilpivirine as Juluca is not approved for use in adolescents, the doses of both dolutegravir and rilpivirine in Juluca are approved for use in adolescents as single drugs. The Panel usually endorses adult formulations for use in adolescents, and this product may be appropriate for certain adolescents. However, because the strategy of treatment simplification has not been evaluated in adolescents who may have difficulties adhering to therapy, the Panel **does not currently recommend** the use of Juluca for adolescents and children until more data are available.

### *Long-Acting, Injectable Rilpivirine*

Currently, a long-acting, injectable formulation of rilpivirine is under development as a treatment for adult patients (in combination with a cabotegravir long-acting injectable).<sup>16</sup> An IMPAACT study of the same regimen in adolescents is expected to begin enrolling participants in 2018.

### *Toxicity*

In the PAINT study, the observed AEs were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, and headache). The incidence of depressive disorders was 19.4% (7/36 participants) compared to 9% in the Phase 3 trials in adults. The incidence of Grades 3 and 4 depressive disorders was 5.6% (2/36 participants).<sup>2</sup>

Six out of 30 adolescents (20%) with a normal adrenocotropic hormone stimulation test at baseline developed an abnormal test during the trial. There were no serious AEs, deaths, or treatment discontinuations attributed to adrenal insufficiency. The clinical significance of abnormal adrenocotropic hormone stimulation tests is not known, but **this finding** warrants further evaluation.<sup>2</sup>

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## **Protease Inhibitors (PIs)**

Atazanavir (ATV, Reyataz)

Darunavir (DRV, Prezista)

Fosamprenavir (FPV, Lexiva)

Indinavir (IDV, Crixivan)

Lopinavir/Ritonavir (LPV/r, Kaletra)

Nelfinavir (NFV, Viracept)

Saquinavir (SQV, Invirase)

Tipranavir (TPV, Aptivus)

# Atazanavir (ATV, Reyataz) (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 Packet:** 50 mg/packet

**Capsules:** 150 mg, 200 mg, and 300 mg

**Fixed-Dose Combination Tablets**

- [Evo<sup>®</sup>taz] Atazanavir 300 mg plus cobicistat 150 mg

## Generic Formulations

**Capsules:** 150 mg, 200 mg, 300 mg

**Capsules and powder packets are not interchangeable.**

## Dosing Recommendations

### Neonate Dose:

- Not approved for use in neonates and infants aged <3 months. Atazanavir should not be administered to neonates due to risks associated with hyperbilirubinemia (kernicterus).

### Pediatric Dose

*Powder Formulation:*<sup>a</sup>

- Powder formulation must be administered with ritonavir.
- Not approved for use in infants aged <3 months or weighing <5 kg.

### Infants and Children (Aged ≥3 Months; Weighing ≥5 kg)

#### Atazanavir Powder<sup>a</sup>

Weight (kg)	Once-Daily Dose
5 kg to <15 kg	Atazanavir 200 mg (4 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food
15 kg to <25 kg <sup>b</sup>	Atazanavir 250 mg (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food

*Capsule Formulation:*<sup>a</sup>

- Not approved for use in children aged <6 years or weighing <15 kg.

## Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first-degree symptomatic atrioventricular block in some patients
- Nephrolithiasis
- Increased serum transaminases
- Hyperlipidemia (primarily with ritonavir boosting)

## Special Instructions

- Administer atazanavir with food to enhance absorption.
- Capsules and powder packets are not interchangeable.
- Do not open capsules.

### Powder Administration:

- Mix atazanavir oral powder with at least 1 tablespoon of food (e.g., applesauce, yogurt). Oral powder mixed with a beverage (at least 30 mL of milk or water) may be used for older infants who can drink from a cup. For young infants (aged <6 months) who cannot eat solid food or drink from a cup, oral powder should be mixed with at least 10 mL of infant formula and given using an oral dosing syringe.
- Administer ritonavir immediately following powder administration.
- Administer the entire dose of oral powder within 1 hour of preparation.
- Because atazanavir can prolong the



## Children (Aged ≥6 Years; Weighing ≥15 kg):

### Atazanavir Capsules<sup>a</sup>

Weight (kg)	Once-Daily Dose
<15 kg	Capsules not recommended
15 kg to <35 kg	Atazanavir 200 mg plus ritonavir <sup>c</sup> 100 mg, both once daily with food
≥35 kg	Atazanavir 300 mg plus ritonavir <sup>c</sup> 100 mg, both once daily with food

#### For Treatment-Naive Pediatric Patients Who Do Not Tolerate Ritonavir:

- Atazanavir powder must be administered with ritonavir.
- For capsule formulation, atazanavir/ritonavir (ATV/r) is preferred for children and adolescents. Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted atazanavir in children aged <13 years. If unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations (see [Pediatric Use](#)).
- Only ATV/r should be used in combination with tenofovir disoproxil fumarate (TDF), because TDF decreases atazanavir exposure.

### Adolescent and Adult Dose

#### Treatment-Naive Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.<sup>d</sup>
- Atazanavir 300 mg plus cobicistat<sup>e</sup> 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Atazanavir/cobicistat is currently not FDA-approved for use in children aged <18 years.
- Atazanavir 400 mg once daily with food. If unboosted atazanavir is used in adolescents, higher doses than those used in adults may be required to achieve target drug concentrations (see [Pediatric Use](#)).

#### Treatment-Experienced Patients:

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.<sup>d</sup>
- Atazanavir 300 mg plus cobicistat<sup>e</sup> 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Atazanavir/cobicistat is currently not FDA-approved for use in children aged <18 years.

electrocardiogram PR interval, use atazanavir with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).

- Atazanavir absorption is dependent on low gastric pH; therefore, when atazanavir is administered with medications that alter gastric pH, special dosing information is indicated (see the Drug Interactions section on the [atazanavir package insert](#)). When administered with buffered didanosine formulations or antacids, give atazanavir at least 2 hours before or 1 hour after antacid or didanosine administration.
- The plasma concentration, and therefore the therapeutic effect, of atazanavir can be expected to decrease substantially when atazanavir is co-administered with proton-pump inhibitors. Antiretroviral therapy-naive patients receiving proton-pump inhibitors should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted atazanavir. Co-administration of atazanavir with proton-pump inhibitors is not recommended in treatment-experienced patients.
- Patients with hepatitis B virus or hepatitis C virus infections and patients with marked elevations in transaminases before treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.
- Atazanavir oral powder contains phenylalanine, which can be harmful to patients with phenylketonuria. Each packet contains 35 mg of phenylalanine.

### Metabolism/Elimination

- Atazanavir is a substrate and inhibitor of cytochrome P (CYP) 3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).

#### Atazanavir Dosing in Patients with Hepatic Impairment:

- Atazanavir should be used with caution in patients with mild or moderate hepatic impairment; consult manufacturer's prescribing information for dose adjustment in patients with moderate impairment.
- Atazanavir should not be used in patients with

*Atazanavir in Combination with Efavirenz (Adults) in Treatment-Naive Patients Only:*

- Atazanavir 400 mg plus ritonavir 100 mg plus efavirenz 600 mg, all once daily at separate times.<sup>d</sup>
- Although ATV/r should be taken with food, efavirenz should be taken on an empty stomach, preferably at bedtime. Efavirenz should not be co-administered with atazanavir (with or without ritonavir) in treatment-experienced patients, because efavirenz decreases atazanavir exposure.

*Atazanavir in Combination with TDF (Adults):*

- Atazanavir 300 mg plus ritonavir 100 mg plus TDF 300 mg, all once daily with food.<sup>d</sup>
- Atazanavir 300 mg plus cobicistat<sup>e</sup> 150 mg plus TDF 300 mg, all once daily with food. **Atazanavir/cobicistat** is currently not **FDA-approved** for use in children aged <18 years.
- Only boosted atazanavir should be used in combination with TDF, because TDF decreases atazanavir exposure.

severe hepatic impairment.

Atazanavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required for patients with renal impairment.
- Atazanavir should not be given to treatment-experienced patients with end-stage renal disease who are on hemodialysis.

<sup>a</sup> mg/kg dosing is higher for the powder packets than for the capsules. Bioavailability was higher for the capsules than for the powder when studied in adults.

<sup>b</sup> For a child weighing  $\geq 25$  kg who cannot swallow atazanavir capsules, atazanavir 300 mg (6 packets) oral powder plus ritonavir 100 mg oral solution, both once daily with food, may be used.

<sup>c</sup> Either ritonavir capsules or ritonavir oral solution can be used.

<sup>d</sup> For adult patients who cannot swallow capsules, atazanavir oral powder is taken once daily with food at the same adult dose as the capsules, along with ritonavir.

<sup>e</sup> See the [cobicistat](#) section for important information about toxicity, drug interactions, and monitoring of patients who receive cobicistat and the combination of cobicistat and TDF.

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

- **Metabolism:** Atazanavir is both a substrate and an inhibitor of the cytochrome P (CYP) 3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. Atazanavir is a weak inhibitor of CYP2C8. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronosyltransferase (UGT1A1). Because there is potential for multiple drug interactions with atazanavir, a patient's medication profile should be carefully reviewed for potential drug interactions before atazanavir is administered.
- **Nucleoside reverse transcriptase inhibitors (NRTIs):** Tenofovir disoproxil fumarate (TDF) decreases atazanavir plasma concentrations. Only atazanavir/ritonavir (ATV/r) should be used in combination with TDF.
- **Non-nucleoside reverse transcriptase inhibitors:** Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be co-administered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be co-administered with atazanavir in treatment-experienced patients, but may be used in combination with atazanavir 400 mg plus ritonavir boosting in treatment-naïve adults.

- *Integrase inhibitors:* Atazanavir is an inhibitor of UGT1A1 and may increase plasma concentrations of raltegravir. This interaction may not be clinically significant.
- *Absorption:* Atazanavir absorption is dependent on low gastric pH. Atazanavir dosage should be adjusted when it is administered with medications that alter gastric pH. Guidelines for dosing atazanavir with antacids, H<sub>2</sub> receptor antagonists, and proton-pump inhibitors in adults are complex and can be found on the [package insert for atazanavir](#). No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.
- Co-administering cobicistat, a CYP3A4 inhibitor, and medications metabolized by CYP3A4 may increase plasma concentrations of these medications. This may increase the risk of clinically significant adverse reactions (including life-threatening or fatal reactions) associated with the concomitant medications. Co-administration of cobicistat with atazanavir in combination with CYP3A4 inducers may lead to lower exposure of cobicistat and atazanavir, loss of efficacy of atazanavir, and possible development of resistance.<sup>1</sup> Co-administration of cobicistat and atazanavir with some antiretroviral (ARV) agents (e.g., with etravirine, with efavirenz in treatment-experienced patients, with another ARV that requires pharmacokinetic [PK] enhancement, such as another protease inhibitor [PI] or elvitegravir) may result in decreased plasma concentrations of that agent, leading to loss of therapeutic effect and 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 PR interval of electrocardiogram (ECG). Abnormalities in atrioventricular (AV) conduction are generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild or moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. The addition of ritonavir to atazanavir is associated with lipid abnormalities, but to a lesser extent than with other boosted PIs.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. **Chronic kidney disease including biopsy-proven cases of granulomatous interstitial nephritis associated with the deposition of atazanavir drug crystals in the renal parenchyma**, nephrolithiasis. Hepatotoxicity (patients with hepatitis B virus or hepatitis C virus infections are at increased 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

Atazanavir is Food and Drug Administration (FDA)-approved for use in infants (aged >3 months and weighing ≥5 kg), children, and adolescents.

#### Efficacy

ATV/r has efficacy equivalent to efavirenz-based and lopinavir/ritonavir (LPV/r)-based combination therapy when given in combination with two NRTIs in treatment-naïve adults.<sup>2-5</sup> In ACTG A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or raltegravir, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, ATV/r was discontinued more frequently than the other regimens due to toxicity, most often hyperbilirubinemia or gastrointestinal complaints.<sup>6</sup>

P1020 enrolled 195 antiretroviral therapy (ART)-naïve and ART-experienced patients with HIV aged

3 months to 21 years. Capsule and powder formulations and boosted and unboosted regimens were investigated in this open-label study; area under the curve (AUC) targeting was used to direct dose finding. Of the 195 patients enrolled, 142 patients received atazanavir-based treatment at the final recommended dose. Among them, 58% were ART-naive. At Week 48, 69.5% of the ART-naive patients and 43.3% of the ART-experienced patients had HIV viral loads  $\leq 400$  copies/mL.<sup>7,8</sup>

Two open-label clinical trials, PRINCE I and PRINCE II, studied a powder formulation of atazanavir administered once daily and boosted with liquid ritonavir in infants and children aged  $\geq 3$  months and weighing  $\geq 5$  kg.<sup>9,10</sup> One hundred and thirty-four infants and children weighing between 5 kg and 35 kg were evaluated. Using a modified intent-to-treat analysis, overall proportions of ARV-naive and ARV-experienced patients with HIV RNA  $< 50$  copies/mL at Week 48 were 54% (28/52) and 50% (41/82), respectively. The median increase from baseline in absolute CD4 T lymphocyte count (percent) at 48 weeks of therapy was 215 cells/mm<sup>3</sup> (6%) in ARV-naive patients and 133 cells/mm<sup>3</sup> (4%) in ARV-experienced patients.

### Pharmacokinetics and Dosing

#### Oral Capsule

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of ritonavir boosting, atazanavir can achieve protocol-defined PK targets—but only when used at higher doses of atazanavir (on a mg/kg body weight or mg/m<sup>2</sup> body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children aged  $> 6$  to  $< 13$  years required atazanavir dosing of 520 mg/m<sup>2</sup> per day of atazanavir capsule formulation to achieve PK targets.<sup>8</sup> Unboosted atazanavir at this dose was well tolerated in those aged  $< 13$  years who were able to swallow capsules.<sup>11</sup> Doses required for older adolescents were greater than the approved dose for adults of atazanavir 400 mg given without ritonavir boosting once daily; adolescents aged  $> 13$  years required atazanavir dosing of 620 mg/m<sup>2</sup> per day.<sup>8</sup> In this study, the AUCs for the unboosted arms were similar to the ATV/r groups but the maximum plasma concentration ( $C_{max}$ ) was higher and the minimum plasma concentration ( $C_{min}$ ) was lower for the unboosted arms. Median doses of atazanavir in mg/m<sup>2</sup> both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150 ng/mL.<sup>12</sup> Higher target trough concentrations may be required in PI-experienced patients. **IMPAACT P1058, a study of unboosted atazanavir PKs in treatment-experienced children, concluded that once-daily atazanavir 400 mg provided suboptimal exposure and that administering higher unboosted doses or splitting the daily dose into twice-daily doses warranted investigation in treatment-experienced children, adolescents, and young adults.**<sup>13</sup>

#### Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A<sup>8</sup>

Age Range (Years)	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	208	200
$> 13$ years	No	620	900
$> 13$ years	Yes	195	350

<sup>a</sup> Dose 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.

**Key to Acronyms:** ATV = atazanavir; AUC = area under the curve; PK = pharmacokinetic; RTV = ritonavir; **TDM = therapeutic drug monitoring**

In the report of the P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m<sup>2</sup> in pediatric subjects when dosed with ritonavir.<sup>14</sup> A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A),<sup>15</sup> **along with subsequent additional adjusted modeling,**<sup>16</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  $\geq 6$  to  $< 18$  years:

- 200/100 mg (15 kg to <35 kg)
- 300/100 mg (≥35 kg)

*Cobicistat as a Pharmacokinetic Enhancer*

A study of 14 adolescents, aged 12 years to 18 years, suggests that cobicistat is a safe and effective PK enhancer when used in combination with atazanavir in adolescent patients.<sup>17</sup>

*Oral Powder*

The unboosted atazanavir powder cohorts in IMPAACT/PACTG P1020A were closed based on the inability to achieve target exposures. For the IMPAACT/PACTG P1020A trial, AUC targets were established based on exposures in adults in early studies of unboosted atazanavir. For that study, target AUC range was 30,000 to 90,000 ng\*hr/mL. Boosted atazanavir powder cohorts in IMPAACT/PACTG P1020A in children aged 3 months to 2 years, using a dose of 310 mg/m<sup>2</sup> daily, achieved average atazanavir exposures that approached but did not meet protocol targets. Variability in exposures was greater, especially among the very young children in this age range.<sup>8</sup>

Assessment of the PK, safety, tolerability, and virologic response of atazanavir oral powder for FDA approval was based on data from 2 open-label, multicenter clinical trials:

- PRINCE I: In pediatric patients aged 3 months to <6 years<sup>9</sup>
- PRINCE II: In 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. All patients in the PRINCE trials were treated with boosted atazanavir and two NRTIs. Patients weighing 5 kg to <10 kg received either 150 mg or 200 mg atazanavir and 80 mg ritonavir oral solution, 10 kg to <15 kg received 200 mg atazanavir and 80 mg ritonavir oral solution, 15 kg to <25 kg received 250 mg atazanavir and 80 mg ritonavir oral solution, and 25 kg to <35 kg received 300 mg atazanavir and 100 mg ritonavir oral solution. No new safety concerns were identified in these trials. The FDA label includes the following PK parameters measured in the PRINCE trials, including mean AUC, for the weight ranges that correspond to the recommended doses:

**Pharmacokinetic Parameters for Atazanavir Powder in Children (PRINCE I and II)<sup>a</sup> versus Capsules in Young Adults<sup>b</sup> and Adults<sup>a</sup>**

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 <sup>a</sup>
	Dose 150/80 (mg) Body Weight (kg) 5 to <10	Dose 200/80 (mg) Body Weight (kg) 5 to <10	Dose 200/80 (mg) Body Weight (kg) 10 to <15	Dose 250/80 (mg) Body Weight (kg) 15 to <25	Dose 300/100 (mg) Body Weight (kg) ≥25 to <35		
<b>AUC ng•h/mL</b> 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]
<b>C24 ng/mL</b> 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> 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 to Acronyms:** ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation; PK = pharmacokinetic; TDF = tenofovir disoproxil fumarate

While the PK targets were met in these PK studies of atazanavir powder in all but the ATV/r 150/80 mg dose in the 5 kg to <10 kg weight band, there were large coefficients of variation (CV)%, especially in the youngest patients.

### *Transitioning from Powder to Capsules*

For children who reach a weight  $\geq 25$  kg while taking the powder, atazanavir 300 mg (6 packets) powder plus ritonavir oral solution 100 mg, both once daily with food, may be used. Atazanavir capsules should be used for children who can swallow pills. Bioavailability was higher for the capsules than for the powder when studied in adults; therefore, a lower mg/kg dose is recommended. Opened capsules have not been studied and should not be used.

### *Toxicity*

Nine percent of patients enrolled in the IMPAACT/PACTG 1020A trial had a bilirubin  $\geq 5.1$  times the upper limit of normal.<sup>11</sup> Asymptomatic ECG abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in one patient, Grade 2 PR or HR changes in nine patients, and Grade 3 PR prolongations in three patients. No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with two NRTIs.<sup>10</sup>

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# Darunavir (DRV, Prezista) (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 Suspension:** 100 mg/mL

**Tablets:** 75 mg, 150 mg, 600 mg, and 800 mg

### Fixed-Dose Combination Tablets

- [Prezcobix] Darunavir 800 mg plus cobicistat 150 mg

## Dosing Recommendations

**Note:** Darunavir should not be used without a pharmacokinetic (PK) enhancer (i.e., boosting agent): ritonavir (for children and adults) or cobicistat (for adults only).

### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

### Pediatric Dose

*Aged <3 Years:*

- **Do not use darunavir in children aged <3 years or weighing  $\leq 10$  kg** because of toxicity concerns based on seizures and death observed in infant rats and attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

*Aged  $\geq 3$  Years:*

- See table below for children aged  $\geq 3$  years who are antiretroviral **treatment-naive and treatment-experienced** with or without 1 or more darunavir resistance-associated mutations.

### Aged 3 to <12 Years and Weighing $\geq 10$ kg

Weight (kg)	Dose (Twice Daily with Food) <sup>a</sup>
10 kg to <11 kg <sup>b</sup>	Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)
11 kg to <12 kg <sup>b</sup>	Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL) <sup>c</sup>
12 kg to <13 kg <sup>b</sup>	Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL) <sup>c</sup>
13 kg to <14 kg <sup>b</sup>	Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL) <sup>c</sup>
14 kg to <15 kg	Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL) <sup>c</sup>
15 kg to <30 kg	Darunavir 375 mg (combination of tablets or 3.8 mL <sup>d</sup> ) plus ritonavir 48 mg (0.6 mL <sup>d</sup> )
30 kg to <40 kg	Darunavir 450 mg (combination of tablets or 4.6 mL <sup>d</sup> ) <sup>e</sup> plus ritonavir (100 mg tablet or 1.25 mL <sup>b</sup> )
$\geq 40$ kg	Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)

## Selected Adverse Events

- Skin rash, including Stevens-Johnson syndrome and erythema multiforme
- Hepatotoxicity
- Diarrhea, nausea
- Headache
- Hyperlipidemia, transaminase elevation, hyperglycemia
- Fat maldistribution

## Special Instructions

- In patients with 1 or more darunavir-associated mutations, darunavir should only be used twice daily. **Darunavir resistance-associated mutations are:** V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
- Darunavir must be administered with food, which increases plasma concentrations by 30%.
- Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergy.
- Pediatric dosing requires co-administration of tablets with different strengths to achieve the recommended doses for each weight band. Careful instructions to caregivers when recommending a combination of different-strength tablets is very important.
- Store darunavir tablets and oral suspension at room temperature (25°C or 77°F). Suspension must be shaken well before dosing.

## Metabolism/Elimination

- Cytochrome (CYP) P450 3A4 inhibitor and substrate.



Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; PK, efficacy, and safety of darunavir/ cobicistat is currently under investigation in children aged 12 to 18 years.

**Adolescent (Weighing  $\geq 40$  kg)<sup>e</sup> and Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations)**

- Darunavir 800 mg (tablet or combination of tablets) plus ritonavir 100 mg **once daily**

**Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations):**

- Darunavir 800 mg (tablet) plus cobicistat<sup>f</sup> 150 mg (tablet) or coformulated as Prezcoibix **once daily with food**

**Adolescent (Weighing  $\geq 30$  to <40 kg; Treatment Naive or Treatment-Experienced with or without at Least 1 Darunavir Resistance-Associated Mutation):**

- Darunavir 450 mg (combination of tablets) plus ritonavir 100 mg both **twice daily with food**

**Adolescent (Weight  $\geq 40$  kg) and Adult Dose (Treatment-Experienced With at Least 1 Darunavir Resistance-Associated Mutation):**

- Darunavir 600 mg plus ritonavir 100 mg, both **twice daily with food**
- The use of cobicistat **is not recommended** with darunavir 600 mg twice daily.

<sup>a</sup> Once-daily dosing is Food and Drug Administration (FDA)-approved, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend it for children (see Frequency of Administration section below).

<sup>b</sup> Note that the dose in children weighing 10 kg to 15 kg is 20 mg/kg darunavir and 3 mg/kg ritonavir per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.

<sup>c</sup> Ritonavir 80 g/mL oral solution.

<sup>d</sup> The **volumes for the** 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

<sup>e</sup> Some Panel members recommend **the FDA-approved dose of** once-daily darunavir 675 mg (combination of tablets) plus ritonavir 100 mg once daily for adolescents weighing  $\geq 30$  kg to <40 kg (**see Table B below**).

<sup>f</sup> See **cobicistat section** for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

Darunavir Dosing in Patients with Hepatic Impairment:

- Darunavir is primarily metabolized by the liver. Caution should be used when administering darunavir to patients with hepatic impairment. Darunavir is not recommended in patients with severe hepatic impairment.

Darunavir Dosing in Patients with Renal Impairment:

- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min).

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

- **Metabolism:** Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Both ritonavir and cobicistat are inhibitors of CYP3A4, thereby increasing the plasma concentration of darunavir. Co-administration of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) with drugs that are highly dependent on CYP3A clearance creates potential for multiple drug-drug interactions and may be associated with serious and/or life-threatening events or suboptimal efficacy.
- Co-administration of several drugs, including protease inhibitors and rifampin, is **contraindicated** with ritonavir- or cobicistat-boosted darunavir. **A recent study involving adults with HIV suggested that etravirine may reduce serum darunavir concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent.**<sup>1</sup> Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

### **Major Toxicities**

- **More common:** Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.
- **Less common:** Skin rash, including erythema multiforme and Stevens-Johnson syndrome, fever and elevated 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*

Darunavir co-administered with ritonavir is approved by the Food and Drug Administration (FDA) as a component of antiretroviral therapy (ART) in treatment-naïve and treatment-experienced children aged  $\geq 3$  years.

#### *Efficacy in Clinical Trials*

- Data from a randomized, open-label, multicenter pediatric trial, which evaluated darunavir co-administered with ritonavir twice daily among 80 treatment-experienced children aged 6 to <18 years, demonstrated that 66% of patients had plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL at Week 24.<sup>2,3</sup>
- In an international, multisite clinical trial (TMC114-TiDP29-C228) involving treatment-experienced children aged 3 to <6 years, 81% of children (17/21) had viral load <50 copies/mL at Week 48.<sup>3,4</sup>

### **Pharmacokinetics and Dosing**

#### *Pharmacokinetics in Children Aged 3 to <6 Years*

Twenty-one children aged 3 to <6 years and weighing 10 kg to <20 kg received twice-daily DRV/r oral suspension. These children had experienced failure of their previous ART regimens and had fewer than three darunavir resistance mutations on genotypic testing.<sup>2-4</sup> The darunavir 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>2-4</sup>

## Pharmacokinetics in Children Aged >6 Years

Initial pediatric pharmacokinetic (PK) evaluation of darunavir tablets and ritonavir liquid 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>5</sup> Part 1 of the trial used a weight-adjusted dose of darunavir 9 mg/kg to 15 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily, equivalent to the standard adult dose of DRV/r 600/100 mg twice daily. This dose resulted in inadequate drug exposure in the pediatric population studied, with 24-hour AUC (AUC<sub>24h</sub>) of 81% and pre-dose concentration (C<sub>0h</sub>) of 91% of the corresponding adult PK parameters. A pediatric dose 20% to 33% higher than the directly scaled adult dose was needed to achieve drug exposure similar to that found in adults, and this was the dose selected for Part 2 of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 mg/kg to 19 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily. This resulted in darunavir AUC<sub>24h</sub> of 123.3 mcg\*h/mL (range 71.9–201.5 mcg\*h/mL) and C<sub>0h</sub> of 3,693 ng/mL (range 1,842–7,191 ng/mL), 102% and 114% of the respective PK values in adults. Doses were given twice daily and were stratified by body weight bands of 20 kg to <30 kg and 30 kg to <40 kg. Based on the findings in the safety and efficacy portion of the study, current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 kg to <40 kg were selected (see Table A).

**Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Backbone (Children Aged 3 Years to 18 Years and Adults Aged >18 Years)**

Population	N	Dose of DRV/RTV	AUC <sub>12h</sub> (mcg*h/mL) Median <sup>a</sup>	C <sub>0h</sub> (ng/mL) Median <sup>a</sup>
10 kg to <15 kg <sup>a</sup>	13	20/3 mg/kg	66.0	3,533
10 kg to <15 kg <sup>a</sup>	4	25/3 mg/kg	116.0	8,522
15 kg to <20 kg <sup>a</sup>	11	20/3 mg/kg	54.2	3,387
15 kg to <20 kg <sup>a</sup>	14	25/3 mg/kg	68.6	4,365
Aged 6 Years to <12 Years <sup>b</sup>	24	Weight bands <sup>b</sup>	56.4	3,354
Aged 12 Years to <18 Years <sup>b</sup>	50	Weight bands <sup>b</sup>	66.4	4,059
Adults Aged >18 Years (3 studies) <sup>c</sup>	285/278/119	600/100 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> Weight band dosing was with DRV/r at doses of 375/50 mg twice daily for body weight 20 kg to <30 kg, 450/60 mg twice daily for 30 kg to <40 kg, and 600/100 mg twice daily for  $\geq 40$  kg. Data from FDA pharmacokinetics review 2008. 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 [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021976s043,202895s017lbletd.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017lbletd.pdf).

**Key to Acronyms:** AUC<sub>12h</sub> = 12-hour area under the curve; C<sub>0h</sub> = pre-dose concentration; DRV = darunavir; DRV/r = darunavir/ritonavir RTV = ritonavir

## Dosing

### Pharmacokinetic Enhancers

Darunavir should not be used without a PK enhancer (boosting agent): ritonavir (for children and adults) or cobicistat (for adults only).

A study in 19 Thai children used the ritonavir 100-mg capsule twice daily as the boosting dose with twice-daily darunavir doses of 375 mg (body weight 20 kg to <30 kg), 450 mg (body weight 30–40 kg), and 600 mg twice daily (body weight  $\geq 40$  kg).<sup>6</sup> The darunavir exposures with 100-mg ritonavir twice daily were similar to those obtained in the studies with lower (<100 mg) liquid-preparation-based ritonavir doses.<sup>5,6</sup> The

tolerability and PK data from this small study support the higher doses of ritonavir boosting with 100-mg capsule or tablet in children weighing  $\geq 20$  kg, particularly when lower-dose formulations are unavailable or if a child does not tolerate the liquid ritonavir formulation. Data are not available to evaluate the safety and tolerability of using ritonavir 100-mg tablet/capsule formulations in children weighing  $< 20$  kg.

Data on the dosing of cobicistat with darunavir are available in adult patients only.<sup>7</sup> Data on a fixed-dose combination of DRV/c 800/150 mg once daily showed comparable bioavailability to that obtained with 800/100 mg of DRV/r once daily.<sup>8</sup>

### Frequency of Administration

In February 2013, the FDA approved the use of once-daily darunavir for treatment-naïve children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). To derive once-daily pediatric dosing recommendations for younger pediatric subjects aged 3 years to  $< 12$  years and weighing 10 kg to  $< 40$  kg, population PK modeling and simulation were used.<sup>3,9</sup> A dedicated pediatric trial evaluating once-daily DRV/r dosing in children aged 6 years to  $< 12$  years was not conducted. No efficacy data have been obtained regarding use of once-daily DRV/r in treatment-naïve or treatment-experienced children aged  $< 12$  years. **Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) generally recommends dosing DRV/r twice daily in children aged  $\geq 3$  years to  $< 12$  years** (see [Once-Daily Dosing](#) section). 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 darunavir resistance-associated mutations. If darunavir and ritonavir are used once daily in children aged  $< 12$  years, the Panel recommends conducting PK (measurement of plasma concentrations) evaluation and closely monitoring viral load.

FDA approval was based on results from two small pediatric trials: TMC114-C230, which evaluated once-daily dosing in treatment-naïve adolescents aged 12 to 18 years and weighing  $\geq 40$  kg (see below), and the TMC114-C228 sub-trial, which evaluated once-daily dosing in treatment-experienced children aged 3 years to  $< 6$  years (see below).<sup>9-11</sup>

### Table B. Food and Drug Administration-Approved Dosing for Pediatric Patients Aged $\geq 3$ Years and Weighing $> 10$ kg who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance-Associated Mutations

**Note:** The Panel generally recommends dosing darunavir with ritonavir twice daily in children aged  $\geq 3$  years to  $< 12$  years.

Weight (kg)	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 or combination of tablets or 6 mL) plus RTV 100 mg (tablet 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 or 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 35 mg/kg DRV and 7 mg/kg RTV per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.

<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 2 administrations (3.4 mL and 4 mL, respectively) with the included oral dosing syringe, or as one syringe when provided by pharmacy or medical office.

**Key to Acronyms:** DRV = darunavir; RTV = ritonavir

### Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg

During the TMC114-C228 trial, the researchers investigated once-daily dosing of darunavir for 2 weeks with PK evaluation in treatment-experienced children aged 3 years to <12 years as part of a sub-study. After the conclusion of the sub-study, the participants switched back to a twice-daily regimen.<sup>9,12</sup> The DRV/r dose for once-daily use in the trial, based on PK simulation (which did not include a relative bioavailability factor), was 40 mg/kg of darunavir co-administered with approximately 7 mg/kg of ritonavir once daily for children weighing <15 kg, and DRV/r 600/100 mg once daily for children weighing ≥15 kg.<sup>9,12</sup> The PK data obtained from 10 children aged 3 to 6 years in this sub-study (Table C) were included as part of the population PK modeling and simulation, which proposed the FDA-approved dose for once-daily DRV/r in children aged 3 years to <12 years. Despite the FDA dosing guidelines, and because of the small set of data used for modeling and the lack of efficacy data on once-daily DRV/r in treatment-naïve or treatment-experienced children aged <12 years, **the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years.**

**Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 Years to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone<sup>12</sup>**

PK Parameter	Once-Daily Darunavir Sub-Study (n = 10) Children Aged 3–6 years	Adult Study (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 to Acronyms:** 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 ≥12 and Weighing ≥40 kg

A sub-study of once-daily dosing of darunavir 800 mg with ritonavir 100 mg in 12 treatment-naïve adolescents (aged 12–17 years and weighing ≥40 kg) demonstrated darunavir exposures similar to those seen in adults treated with once-daily darunavir (see Table D).<sup>10</sup> In this study, the proportion of patients with viral load <50 copies/mL and <400 copies/mL at 48 weeks was 83.3% and 91.7%, respectively.<sup>11</sup> Interestingly, no relationship was observed between darunavir AUC<sub>24h</sub> and C<sub>0h</sub> and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those in adults with once-daily dosing in another study in which a single dose of darunavir 800 mg with ritonavir 100-mg tablets was administered to 24 subjects with median age 19.5 years (range 14–23 years).<sup>13</sup> However, darunavir exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting the potential need for higher doses in younger adolescents. A single case report suggests the potential therapeutic benefit of virologic suppression using an increased darunavir dose with standard ritonavir booster following therapeutic drug monitoring (TDM) in a highly treatment-experienced adolescent patient.<sup>14</sup>

**Table D. Darunavir Pharmacokinetics with Once-Daily Administration (Adolescents Aged ≥12 Years and Adults Aged >18 Years)**

Population	N	Dose of DRV/RTV	AUC <sub>24h</sub> <sup>a</sup> (mcg*h/mL) median	C <sub>0h</sub> (ng/mL) median
<b>Aged 12–17 Years</b> (mean 14.6 years) <sup>10</sup>	12	800/100 mg	86.7	2,141
<b>Aged 14–23 Years</b> (mean 19.5 years) <sup>13</sup>	24	800/100 mg	69.5	1,300
<b>Adults Aged &gt;18 Years</b> (2 studies) <sup>a</sup>	335/280	800/100 mg	87.8–87.9	1,896–2,041

<sup>a</sup> Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021976s043.202895s0171bledt.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043.202895s0171bledt.pdf).

**Key to Acronyms:** AUC<sub>24h</sub> = 24-hour area under the curve; C<sub>0h</sub> = pre-dose concentration; DRV = darunavir; RTV = ritonavir

The efficacy of once-daily darunavir has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.<sup>11,15</sup>

### ***Co-Administration with Other Antiretrovirals***

#### *Nucleotide Reverse Transcriptase Inhibitor*

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 darunavir exposures were lower than those found in adults treated with the same combination.<sup>16</sup> No dose adjustment is recommended for use of the combination of DRV/r with either of these drugs, but caution is advised and therapeutic drug monitoring (TDM) may be potentially useful.

#### *Non-Nucleoside Reverse Transcriptase Inhibitors*

Data from the IMPAACT protocol P1058A report that the co-administration of once-daily DRV/r with etravirine administered once or twice daily to children, adolescents, and young adults aged 9 through <24 years did not have a significant effect on darunavir plasma exposure.<sup>17</sup> When DRV/r was co-administered with etravirine twice daily in pediatric patients, target concentrations for both darunavir and etravirine were achieved.<sup>18</sup> When co-administered once daily, darunavir PKs have not been affected by co-administration of rilpivirine in adolescents and young adults.<sup>19</sup> DRV/r co-administration increased rilpivirine exposure two- to three-fold, indicating that drug-related adverse effects should be closely monitored.

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# Fosamprenavir (FPV, Lexiva) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

## Formulations

**Tablets:** 700 mg

**Oral Suspension:** 50 mg/mL

## Dosing Recommendations

### Pediatric Dose (Aged >6 Months to 18 Years):

- Unboosted fosamprenavir (without ritonavir) is Food and Drug Administration (FDA)-approved for antiretroviral (ARV)-naive children aged 2 to 5 years, but not recommended by the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants  $\geq 4$  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 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.

<b>Population</b>	<b>Dose</b>	<b>AUC<sub>0-24h</sub> (mcg*hr/mL) Except Where Noted</b>	<b>C<sub>min</sub> (mcg/mL)</b>
<b>Infants Aged <math>&lt; 6</math> Months</b>	FPV 45 mg/kg plus RTV 10 mg/kg twice daily	26.6 <sup>a</sup>	0.86
<b>Children Aged 2 Years to <math>&lt; 6</math> Years</b>	FPV 30 mg/kg twice daily (no RTV)	22.3 <sup>a</sup>	0.513
<b>Children Weighing <math>&lt; 11</math> kg</b>	FPV 45 mg/kg plus RTV 7 mg/kg twice daily	57.3	1.65
<b>Children Weighing 15 kg to <math>&lt; 20</math> kg</b>	FPV 23 mg/kg FPV plus RTV 3 mg/kg twice daily	121.0	3.56
<b>Children Weighing <math>\geq 20</math> kg</b>	FPV 18 mg/kg plus RTV 3 mg/kg twice daily (maximum 700/100 mg)	72.3–97.9	1.98–2.54
<b>Adults</b>	FPV 1400 mg twice daily (no RTV)	33	0.35
<b>Adults</b>	FPV 1400 mg plus RTV 100–200 mg RTV once daily	66.4–69.4	0.86–1.45
<b>Adults</b>	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.

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## Indinavir (IDV, Crixivan) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Capsules:** 100 mg, 200 mg, and 400 mg

### Dosing Recommendations

#### Neonate and Infant Dose:

- Not approved for use in neonates/infants.
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

#### Pediatric Dose:

- Not approved for use in children.
- A range of indinavir doses (234–500 mg/m<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 (≥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 (higher 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>

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## Lopinavir/Ritonavir (LPV/r, Kaletra) (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:

- [Kaletra] Lopinavir 80 mg plus 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 plus ritonavir 25 mg
- [Kaletra] Lopinavir 200 mg plus ritonavir 50 mg

### Dosing Recommendations

#### Neonatal Dose (Aged <14 Days):

- No data on appropriate dose or safety in this age group. Do not administer to neonates before a post-menstrual age of 42 weeks and a postnatal age of at least 14 days due to potential toxicities.

#### Dosing for Individuals not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

##### Infant Dose (Aged 14 Days–12 Months):

- Once-daily dosing **is not recommended**.
- Lopinavir/ritonavir (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. **Note:** This dose in infants aged <12 months is associated with lower lopinavir trough levels than those found in adults; lopinavir dosing should be adjusted for growth at frequent intervals (see text below). Also see text for transitioning infants to lower mg per m<sup>2</sup> dose.

##### Pediatric and Adolescent Dose (Aged >12 Months to 18 Years):

- 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

### Selected Adverse Events

- Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhea, taste alteration
- Hyperlipidemia, especially hypertriglyceridemia
- Elevated transaminases
- Hyperglycemia
- PR interval prolongation
- QT interval prolongation and Torsades de Pointes
- Risk of toxicity—including life-threatening cardiotoxicity—is increased in premature infants (see Major Toxicities below).

### Special Instructions

- LPV/r tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- LPV/r tablets must be swallowed whole. **Do not crush or split tablets.**
- LPV/r oral solution should be administered with food because a high-fat meal increases absorption.
- The poor palatability of LPV/r oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- LPV/r oral solution can be kept at room temperature up to 77° F (25° C) if used within 2 months. If kept refrigerated (2° C to 8° C or 36° F to 46° F), LPV/r oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing **is not recommended**

the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

- LPV/r 230 mg/57.5 mg per m<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 lopinavir susceptibility.

#### Weight-Band Dosing for Lopinavir/Ritonavir 100 mg/25 mg Pediatric Tablets for 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> /dose given twice daily	230 mg/m <sup>2</sup> /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> Four of the LPV/r 100 mg/25 mg tablets can be substituted with two tablets each containing LPV/r 200 mg/50 mg in children capable of swallowing a larger tablet.

<sup>b</sup> In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, weighing >45 kg, the Food and Drug Administration (FDA)-approved adult dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing.

#### Adult Dose (Aged >18 Years):

- 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 or adolescents, or in patients receiving concomitant therapy with nevirapine, efavirenz, fosamprenavir, or nelfinavir, or in patients with three or more lopinavir-associated mutations (see Special

because of considerable variability in plasma concentrations in children aged <18 years and a higher incidence of diarrhea.

- Use of LPV/r once daily is specifically **contraindicated** if three or more of the following lopinavir resistance-associated substitutions are present: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. This is because higher lopinavir trough concentrations may be required to suppress resistant virus.

#### Metabolism/Elimination

- Cytochrome P (CYP) 3A4 inhibitor and substrate.

#### LPV/r Dosing in Patients with Hepatic Impairment:

- LPV/r is primarily metabolized by the liver. Use caution when administering lopinavir to patients with hepatic impairment. No dosing information is currently available for children or adults with hepatic insufficiency.
- In the co-formulation of LPV/r, the ritonavir acts as a pharmacokinetic enhancer, not as an ARV agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.



Instructions for list).

In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):

- LPV/r 400 mg/100 mg twice daily

Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir:

**Note:** These drugs induce lopinavir metabolism and reduce lopinavir plasma levels. Increased LPV/r dosing is required with concomitant administration of these drugs.

- Once-daily dosing **should not be used**.

*Pediatric Dose (Aged >12 Months to 18 Years):*

- 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 Dose (Aged >18 Years):*

- FDA-approved dose is LPV/r 500 mg/125 mg twice daily, given as a combination of two tablets of LPV/r 200 mg/50 mg and one tablet of LPV/r 100 mg/25 mg. Alternatively, three tablets of LPV/r 200 mg/50 mg can be used for ease of dosing. Once-daily dosing **should not be used**.

LPV/r Used in Combination with Saquinavir Hard-Gel Capsules or in Combination with Maraviroc:

- Saquinavir and maraviroc doses may need modification (see the [Saquinavir](#) and [Maraviroc](#) sections for more information). **The combination of saquinavir and LPV/r is not recommended.**

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

- *Metabolism:* Cytochrome P (CYP) 3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions with lopinavir/ritonavir (LPV/r).
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with LPV/r. In patients treated with LPV/r, fluticasone (a commonly used inhaled and intranasal steroid) should be avoided and an alternative used. Drug interactions with anti-tuberculous drugs are common and may require dose adjustments or regimen change.

### **Major Toxicities**

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, **insulin resistance**,<sup>1</sup> and hyperlipidemia, especially hypertriglyceridemia,<sup>2</sup> possibly more pronounced in girls than boys.<sup>3</sup> These adverse events may be exacerbated by the higher dose of ritonavir used for boosting with lopinavir (200 mg) compared with atazanavir and darunavir (100 mg).
- *Less common (more severe):* Fat maldistribution.

- *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, and hepatitis (life-threatening in rare cases). PR interval prolongation, QT interval prolongation, and Torsades de Pointes may occur.
- *Special populations—neonates:* LPV/r **should not be used** during the immediate postnatal period in premature infants because an increased risk of toxicity in premature infants has been reported. These toxicities in premature infants include transient symptomatic adrenal insufficiency,<sup>4</sup> life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),<sup>5-7</sup> lactic acidosis, acute renal failure, central nervous system depression, and respiratory depression. These toxicities may be from the drug itself and/or from the inactive ingredients in the oral solution, including propylene glycol 15.3% and ethanol 42.4%.<sup>7</sup> Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with LPV/r.<sup>4</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 Food and Drug Administration (FDA)-approved for use in children. **Because there is a risk of toxicity, LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.** Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

#### *Efficacy*

Clinical trials of treatment-naïve adults have shown that regimens containing LPV/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) are comparable to a variety of other regimens including regimens that contain atazanavir, darunavir (at 48 weeks), fosamprenavir, saquinavir/ritonavir, or efavirenz. Studies have also shown that regimens containing LPV/r plus two NRTIs are superior to regimens containing nelfinavir and inferior to regimens containing darunavir (at 192 weeks).<sup>8-16</sup>

LPV/r has been studied in both antiretroviral (ARV)-naïve and ARV-experienced children and has demonstrated durable virologic activity and **acceptable** toxicity.<sup>17-25</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 appropriate pediatric dose would be approximately LPV/r 230 mg/57.5 mg per m<sup>2</sup>. However, younger children have enhanced lopinavir clearance and need higher drug doses to achieve drug exposures similar to those 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. Lopinavir exposures in infants<sup>19,24,26</sup> are compared to those in older children<sup>17</sup> and adults<sup>27</sup> in Table A below.

**Table A. Pharmacokinetics of Lopinavir/Ritonavir by Age**

	Adults <sup>27</sup>	Children <sup>17</sup>	Children <sup>17</sup>	Infants <sup>a</sup> at 12 Months <sup>24</sup>	Infants 6 Weeks–6 Months <sup>19</sup>	Infants 14 Days to <6 Weeks <sup>26</sup>
N	19	12	15	20	18	9
Dose LPV	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 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> Data generated in a study that was cited but not reported in final manuscript. Data in table source: personal communication from Edmund Capparelli, PharmD (April 18, 2012)

**Note:** Values are means; all data shown performed in the absence of non-nucleoside reverse transcriptase inhibitors (NNRTIs).

**Key to Acronyms:** AUC = area under the curve; LPV = lopinavir

Models suggest that diet, body weight, and postnatal age are important factors in lopinavir PK, with improved bioavailability as dietary fat increases over the first year of life<sup>28</sup> and with clearance slowing by age 2.3 years.<sup>29</sup> A study from the U.K. and Ireland compared outcomes of LPV/r treatment with either a 230 mg/m<sup>2</sup>/dose or a 300 mg/m<sup>2</sup>/dose in children aged 5.6 to 12.8 years at the time of LPV/r initiation. Study findings suggested that the higher doses were associated with improved long-term viral load suppression.<sup>30</sup>

### Pharmacokinetics and Dosing

#### 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 both per m<sup>2</sup> of body surface area when compared to LPV/r 300 mg/75 mg per m<sup>2</sup> of body surface area per dose twice daily (see table).<sup>16</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 given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the FDA-recommended 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” 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 would continue the infant dose (300 mg/m<sup>2</sup> of body surface area per dose twice daily) while on LPV/r liquid formulation.

#### 14 Days to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)

The PK of the oral solution at approximately LPV/r 300 mg/75 mg per m<sup>2</sup> body surface area per dose twice daily was evaluated in infants aged <6 weeks<sup>26</sup> and infants aged 6 weeks to 6 months.<sup>19</sup> Even at this higher dose, C<sub>trough</sub> levels were highly variable but 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, lopinavir area under the curve (AUC) was similar to that found in older children.<sup>24</sup> Because infants grow rapidly in the first months of life, it is important to optimize lopinavir dosing by adjusting the dose at frequent intervals. Given the safety of doses as high as 400 mg/m<sup>2</sup> body surface area in older children and adolescents,<sup>20</sup> some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m<sup>2</sup> body surface area dose to allow for projected growth between clinic appointments.

#### Pharmacokinetics and Dosing with Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

In both children and adults, the lopinavir C<sub>trough</sub> is reduced by concurrent treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs) or concomitant fosamprenavir or nelfinavir. Higher doses of lopinavir are

recommended if the drug is given in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir. In 14 children treated with LPV/r 230 mg/57.5 mg per m<sup>2</sup> body surface area per dose twice daily plus nevirapine, the mean lopinavir C<sub>trough</sub> was 3.77 ± 3.57 mcg/mL.<sup>17</sup> Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/r, but the variability in concentration is much higher in children than in adults.<sup>17,31</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> body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily, there was a 34-fold interindividual variation in lopinavir trough concentrations. Five of 15 children (33%) had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.<sup>32</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> body surface area twice daily plus efavirenz 350 mg/m<sup>2</sup> body surface area once daily showed only one patient (6.6%) with sub-therapeutic lopinavir trough concentrations,<sup>33</sup> perhaps because the trial used an efavirenz dose that was approximately 11 mg/kg body weight<sup>33</sup> instead of the 14 mg/kg body weight dose used in the trial discussed above.<sup>32</sup>

## Dosing

### Once Daily

Once-daily dosing of LPV/r 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV in therapy-naive adults aged >18 years. However, once-daily administration **cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM), although this approach may be successful in select, closely monitored children.**<sup>34</sup> There is high interindividual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus, as demonstrated in studies of ARV-naive children and adolescents.<sup>35-38</sup> The **currently available** tablet formulation of LPV/r has lower variability in trough levels than the **previously used** soft-gel formulation.<sup>38,39</sup> An international, randomized, open-label trial designed to demonstrate noninferiority in viral suppression between once-daily and twice-daily LPV/r dosing in children (median [IQR] age of 11 years [with a range of 9–14 years]) was unsuccessful, and more children on once-daily dosing had viral loads ≥50 copies/mL within 48 weeks.<sup>40</sup>

### Dosing and Its Relation to Efficacy

LPV/r is effective in treatment-experienced patients with severe immune suppression,<sup>41,42</sup> although patients with greater prior exposure to ARVs may be slower to reach undetectable viral load concentrations<sup>42,43</sup> and may have less-robust CD4 T lymphocyte (CD4) percentage responses.<sup>44</sup> Twice daily doses of lopinavir used in treatment-experienced patients were 230 mg to 300 mg/m<sup>2</sup> body surface area in 39% of patients, 300 mg to 400 mg/m<sup>2</sup> body surface area in 35%, and greater than 400 mg/m<sup>2</sup> body surface area per dose in 4%.<sup>44</sup>

More important than viral resistance to lopinavir is the relationship of the drug exposure to the susceptibility of the HIV-1 isolate (EC<sub>50</sub>). 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 the C<sub>trough</sub> or EC<sub>50</sub> alone.<sup>45-47</sup> A study of the practical application of the IQ to guide therapy using higher doses of LPV/r in children and adolescents to reach a target IQ of 15 showed the safety and tolerability of doses of LPV/r 400 mg/100 mg per m<sup>2</sup> body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine, or efavirenz) and LPV/r 480 mg/120 mg per m<sup>2</sup> body surface area per dose twice daily (with nevirapine or efavirenz).<sup>20</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 previously treated with protease inhibitors.<sup>48</sup> **A lopinavir plasma concentration of ≥1 mcg/mL is cited as a minimum target trough concentration,<sup>49-51</sup> but this concentration may not adequately control viremia in patients with multiple lopinavir mutations.<sup>52,53</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 of the taste buds with ice chips before or after administration of the solution, masking of the taste by administration with sweet or tangy foods (e.g., chocolate syrup or peanut butter), or having the pharmacist flavor the solution prior to dispensing are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.<sup>54,55</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,  $C_{max}$ , and  $C_{trough}$  compared with swallowing the whole tablet. The variability of the reduced exposure with the crushed tablets (5% to 75% reduction in AUC) means that a dose modification cannot be relied on to overcome the reduced absorption. Crushed tablets cannot be recommended for use.<sup>56</sup> In a PK study using a generic adult formulation of LPV/r manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir  $C_{trough}$  measurements.<sup>39</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>22,57-61</sup> However, one study did not observe this difference in the effect of LPV/r on CD4 cell count,<sup>62</sup> and another study found that the difference did not persist after a year of therapy.<sup>25</sup> Some studies found no differences in the weight gain of children treated with LPV/r versus efavirenz.<sup>60,63</sup> Switching to efavirenz-based ART at or after age 3 years removed the risk of lopinavir-associated metabolic toxicity, with no loss of virologic control (see Table 16 of [Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy](#)).<sup>60,61</sup> Bone mineral density improved when children were treated with efavirenz-containing ART instead of LPV/r-containing ART.<sup>64</sup>

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## Nelfinavir (NFV, Viracept) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Tablets:** 250 mg and 625 mg

#### Dosing Recommendations

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV **no longer recommends** nelfinavir-based regimens for use in children due to inferior potency compared to other regimens.

##### Neonate and Infant Dose:

- Nelfinavir should not be used for treatment in children aged <2 years.

##### Pediatric Dose (Aged $\geq 2$ 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.

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## Saquinavir (SQV, Invirase) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Capsules:** 200 mg

**Tablets:** 500 mg

### Dosing Recommendations

#### Pediatric Dose:

- Not approved for use in **infants**, children, and adolescents aged <16 years.

#### Adolescent and Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg twice daily

### Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (Torsades de Pointes)

### Special Instructions

- Administer within 2 hours after a full meal.
- Sun exposure can cause photosensitivity reactions; advise patients to use sunscreen or protective clothing.
- Pre-therapy electrocardiogram is recommended; saquinavir is **contraindicated** in patients with a prolonged QT interval.

### Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) substrate and inhibitor
- 90% metabolized in the liver
- Use saquinavir **with caution** in patients who have hepatic impairment; **no dose adjustment recommended**.

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

- Saquinavir is both a substrate and inhibitor of the cytochrome P 450 3A4 (CYP3A4) system. Potential exists for multiple drug interactions. Co-administration of saquinavir is **contraindicated** with drugs that are highly dependent on CYP3A clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions.

### Major Toxicities

- *More common:* Diarrhea, abdominal discomfort, headache, nausea, paresthesia, skin rash, and lipid

abnormalities.

- *Less common (more severe)*: Exacerbation of chronic liver disease, lipodystrophy.
- *Rare*: New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in patients with hemophilia, pancreatitis, and elevation in serum transaminases. Saquinavir administered with ritonavir can lead to prolonged QT and/or PR intervals with potential for heart block and ventricular tachycardia (Torsades de Pointes).

### **Resistance**

The International 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*

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 efficacy data were generated at saquinavir doses <50 mg/kg in pediatric trials.**

#### *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.**

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## Tipranavir (TPV, Aptivus) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Oral Solution:** 100 mg tipranavir/mL, with 116 International Units (IU) vitamin E/mL

**Capsules:** 250 mg

### Dosing Recommendations

**Note:** Tipranavir must be boosted with ritonavir. The ritonavir boosting dose used for tipranavir is higher than the doses used for other protease inhibitors.

#### Pediatric (Aged <2 Years) Dose:

- Not approved for use in children aged <2 years

#### Pediatric (Aged 2–18 Years) Dose:

**Note:** Not recommended for treatment-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>

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## Entry and Fusion Inhibitors

Enfuvirtide (T-20, Fuzeon)

Maraviroc (MVC, Selzentry)

## 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>

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# Maraviroc (MVC, Selzentry) (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:** 25 mg, 75 mg, 150 mg, and 300 mg

**Oral Solution:** 20 mg/mL

## Dosing Recommendations

### Neonate and Infant Dose:

- Not approved for use in neonates or infants

### Pediatric Dose:

- Approved for use in treatment-experienced children aged  $\geq 2$  years and weighing  $\geq 10$  kg

### 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	Liquid 20 mg/mL	Tablets
When given with potent cytochrome P (CYP) 3A inhibitors (with or without a potent CYP3A inducer), including elvitegravir/ritonavir (EVG/r) and 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	4 mL	One 75-mg tablet
30 kg to <40 kg	100 mg	5 mL	One 25-mg tablet and one 75-mg tablet
>40 kg	150 mg	7.5 mL	One 150-mg tablet
When given with nucleoside reverse transcriptase inhibitors (NRTIs), enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers:			
10 kg to <20 kg	Not recommended		
20 kg to <30 kg	Not recommended		
30 kg to <40 kg	300 mg	15 mL	One 300-mg tablet
>40 kg	300 mg	15 mL	One 300-mg tablet
When given with potent CYP3A inducers including efavirenz and etravirine (without a potent CYP3A inhibitor):			
Children in all weight bands	Not recommended		

## Selected Adverse Events

- Nausea, vomiting
- Abdominal pain, diarrhea
- Cough
- Upper respiratory tract infections
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally seen in patients with severe renal insufficiency)
- Dizziness

## Special Instructions

- Maraviroc is recommended for patients with only CCR5-tropic HIV-1. Conduct testing with HIV tropism assay (see [Drug-Resistance Testing](#) in the [Adult and Adolescent Guidelines](#)) before using maraviroc to exclude the presence of CXCR4-tropic or mixed/dual-tropic HIV. Do not use maraviroc if CXCR4-tropic or mixed/dual-tropic HIV is present.
- Maraviroc can be given without regard to food.
- Instruct patients on how to recognize symptoms of allergic reactions or hepatitis.
- Use caution when administering maraviroc to patients with underlying cardiac disease.

## Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) substrate

### Maraviroc Dosing in Patients with Hepatic Impairment:

- Use caution when administering maraviroc to patients with hepatic impairment; maraviroc concentrations may be increased.



### Recommended Adult Maraviroc Dose: Tablets

When Co-Administered With:	Dose
Potent CYP3A inhibitors (with or without a potent CYP3A inducer) including PIs (except TPV/r) and EVG/r	150 mg twice daily
NRTIs, enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers	300 mg twice daily
Potent CYP3A inducers, including efavirenz and etravirine (without a potent CYP3A inhibitor)	600 mg twice daily

### Maraviroc Dosing in Adolescents and Adults with Renal Impairment:

- Refer to the manufacturer's prescribing information.
- Data are insufficient to make dosing recommendations for use of maraviroc in children concomitantly receiving noninteracting medications and weighing <30 kg or in all children concomitantly receiving potent CYP3A inducers without a potent CYP3A inhibitor.

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

- **Absorption:** Absorption of maraviroc is slightly reduced with ingestion of a high-fat meal. There were no food restrictions in the adult trials (which used the tablet formulation) and in the pediatric trial (which used both tablet and oral solution formulations) that demonstrated the efficacy, antiviral activity, and safety of maraviroc. Therefore, maraviroc can be given with or without food.
- **Metabolism:** Maraviroc is a cytochrome P (CYP) 3A and p-glycoprotein (P-gp) substrate and requires dose adjustments when administered with CYP- or P-gp-modulating medications. A patient's medication profile should be carefully reviewed for potential drug interactions before administration of maraviroc; recommended maraviroc doses are based on concomitant medications and their anticipated effect on maraviroc metabolism.

### Major Toxicities

- **More common:** Cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, **vomiting, diarrhea**, and headache. Dizziness is **seldom reported in children**.
- **Less common (more severe):** Hepatotoxicity that may be preceded by evidence of a systemic allergic reaction (such as pruritic rash, eosinophilia, or elevated immunoglobulin) has been reported. Serious adverse events (AEs) occurred in <2% of maraviroc-treated adult patients and included cardiovascular abnormalities (e.g., angina, heart failure, myocardial infarction), hepatic cirrhosis or failure, cholestatic jaundice, viral meningitis, pneumonia, myositis, osteonecrosis, and rhabdomyolysis.

### Resistance

HIV tropism assay should be performed before use. Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants. The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#).

### Pediatric Use

#### Approval

Maraviroc 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>

#### Pharmacokinetics and Efficacy

The pharmacokinetics, safety, and efficacy of maraviroc were examined in an international dose-finding and efficacy study (**A4001031**) that involved treatment-experienced children (aged 2 years to **<18** years and

weighing  $\geq 10$  kg) who had HIV-1 plasma RNA  $> 1,000$  copies/mL. Fifty-one percent of the 103 children who participated in the study had HIV-1 subtype C, 25% had subtype B, and 23% had other subtypes.

In this trial, the maraviroc dose was based on body surface area and the composition of the optimized background therapy. Most participants (90/103 participants, or 87%) received maraviroc in combination with potent CYP3A inhibitors, 10 participants received maraviroc with noninteracting medications, and only three participants received maraviroc with CYP3A inducers (without CYP3A inhibitors). The key pharmacologic target (geometric mean  $C_{\text{average}}$  of  $> 100$  ng/mL) was achieved with both the tablet and oral solution formulations of maraviroc.<sup>2</sup>

From a mean baseline plasma HIV-1 RNA 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 maraviroc-related AEs through 48 weeks were diarrhea (16.5%), vomiting (16.5%), and upper respiratory infections (13.6%). At Week 48, 48% of participants had HIV-1 RNA  $< 48$  copies/mL.<sup>3</sup> Of the participants on long-term follow-up at Week 144, 86% had HIV-1 RNA levels of  $< 48$  copies/mL.<sup>2</sup>

## References

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## **Integrase Inhibitors**

Bictegravir (BIC)

Dolutegravir (DTG, Tivicay, GSK1349572)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

## Bictegravir (BIC) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Note:** Bictegravir is only available in a fixed-dose combination tablet.

#### Fixed-Dose Combination Tablet:

- [Biktarvy] Bictegravir 50 mg plus emtricitabine 200 mg plus tenofovir alafenamide (TAF) 25 mg

### Dosing Recommendations

#### [Biktarvy] Bictegravir plus Emtricitabine plus TAF

##### Pediatric/Adolescent Dose (Aged <18 Years):

- Biktarvy has not been Food and Drug Administration-approved for use in patients aged <18 years.
- *Children Aged <12 Years:* No data on appropriate dose of Biktarvy in children age <12 years.
- *Children and Adolescents (Aged ≥12–18 Years and Weighing ≥35 kg):* 1 tablet once daily. This is an **investigational dose**.

##### Adult Dose (Aged ≥18 Years):

- 1 tablet once daily in ART-naive patients. This Biktarvy dose can also be used to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy.

### Selected Adverse Events

- Diarrhea, nausea, headache

#### TAF-Associated Adverse Events:

- Increases in low-density lipoprotein cholesterol and total cholesterol levels

### Special Instructions

- Administer with or without food.
- Screen patients for hepatitis B virus (HBV) infection before use of emtricitabine or TAF. Severe acute exacerbation of HBV can occur when emtricitabine or TAF is discontinued; therefore, monitor hepatic function for several months after halting therapy with emtricitabine or TAF.
- Biktarvy is not recommended for use with other ARV drugs.
- See the [emtricitabine](#) and [TAF](#) sections of the [Drug Appendix](#) for special instructions and additional information about the individual drug components of Biktarvy.

### Metabolism/Elimination

- Bictegravir is metabolized by cytochrome P (CYP) 450 3A and uridine diphosphate glucuronosyltransferase (UGT) 1A1.
- Refer to the [emtricitabine](#) and [TAF](#) sections of the [Drug Appendix](#) for more information on these components of Biktarvy.

#### Biktarvy Dosing in Patients with Hepatic Impairment:

- Biktarvy **is not recommended** for use in patients with estimated creatinine clearance <30 mL/min.

#### Biktarvy Dosing in Patients with Renal Impairment:

- Biktarvy **is not recommended** for use in patients with severe hepatic impairment

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

- **Metabolism:** Bictegravir is a substrate of cytochrome P 3A and uridine diphosphate glucuronosyltransferase (UGT) 1A1. Tenofovir alafenamide (TAF) is a substrate of P-glycoprotein and UGT1A1. Co-administration of bictegravir/emtricitabine/TAF (a fixed-dose combination [FDC] drug marketed under the brand name Biktarvy) and rifampin is **contraindicated**.<sup>1,2</sup>
- **Renal effects:** Bictegravir is an inhibitor of OCT2 and MATE1, so it decreases tubular secretion of creatinine. This increases serum creatinine and reduces estimated glomerular filtration rate with no change in glomerular function. Drugs that decrease renal function could reduce clearance of emtricitabine.
- **Absorption:** Administering bictegravir concurrently with antacids lowers the plasma concentrations of bictegravir. This is due to formation of complexes in the gastrointestinal tract, and not because of changes in gastric pH. It is best to administer Biktarvy, which contains bictegravir, at least 2 hours, but preferably 4 hours, before administering antacids. Chelation by high concentrations of divalent cations, such as iron, decreases absorption of integrase strand transfer inhibitors (INSTIs), including elvitegravir and bictegravir. For this reason, Biktarvy should be administered at least 4 hours before or after iron supplements or multivitamins containing iron. Biktarvy **is not recommended** for use with other antiretroviral (ARV) drugs.

## **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> Creatine kinase elevations can occur.
- **Less common (more severe):** Severe immune reconstitution inflammatory syndrome may be more common with INSTIs than with other ARV agents.

## **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation. Bictegravir, dolutegravir, and cabotegravir, the “second-generation” INSTIs, have higher barriers to resistance than the first-generation INSTIs raltegravir and elvitegravir<sup>3,4</sup> and may have more activity against non-B subtypes of HIV-1.<sup>5</sup>

## **Pediatric Use**

### *Approval*

Bictegravir is not approved for use in children or adolescents. Bictegravir was Food and Drug Administration-approved in 2018 for use in adults who have no ARV treatment history. It is also approved to replace the current ARV regimen in patients who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable ARV regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of the FDC product Biktarvy, which contains 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of TAF.<sup>2</sup>

### *Efficacy in Clinical Trials*

In a short-term Phase 1 study, bictegravir monotherapy at doses of 50 mg or 100 mg was well tolerated and led to HIV-1 RNA <50 copies/mL within 11 days in three out of eight participants in both of these dosing groups.<sup>6</sup> Two Phase 3 randomized trials in ARV treatment-naïve adults showed that Biktarvy had similar efficacy (viral load suppression [VLS] to HIV-1 RNA <50 copies/mL) and safety (incidence of study drug discontinuation [SDD] or death) to comparator regimens. VLS occurred in 89% of participants who received coformulated bictegravir 50 mg, emtricitabine 200 mg, and TAF 25 mg (BIC/FTC/TAF; N = 320) and in 93% of participants who received a regimen of dolutegravir/emtricitabine 50 mg/200 mg and TAF 25 mg (N = 325). SDD occurred in 1% of participants in both groups. In a separate trial, VLS occurred in 92% of participants who received BIC/FTC/TAF (N = 314) and in 93% of participants who received coformulated abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) 600 mg/50 mg/300 mg (N = 315). SDD was not reported for any of the participants receiving

BIC/FTC/TAF, though SDD did occur in 1% of participants receiving ABC/DTG/3TC.<sup>2,8</sup> Studies that randomized virologically suppressed patients on stable ARV regimens to either continue their current regimens or switch to coformulated BIC/FTC/TAF have shown that BIC/FTC/TAF has similar safety and efficacy to existing regimens. VLS occurred in 94% of participants who were randomized to switch to BIC/FTC/TAF (N = 282) and in 95% of participants who continued taking ABC/DTG/3TC (N = 281). SDD was reported in 2% of participants and 1% of participants, respectively. Ninety-two percent of participants who were randomized to switch to BIC/FTC/TAF (N = 290) achieved VLS, while 89% of participants who continued receiving atazanavir- or darunavir-based combination ARV regimens (N = 287) achieved VLS. SDD occurred in 1% of participants in both of these groups.<sup>2</sup>

### Formulations

Bictegravir is only available in the coformulated tablet Biktarvy, which contains bictegravir, emtricitabine, and TAF.

### Use of Biktarvy in Adolescents Aged 12 Years to 18 Years

The adult dosage formulation of Biktarvy (BIC/FTC/TAF 50 mg/200 mg/25 mg) was administered to adolescents aged 12 to <18 years and weighing  $\geq 35$  kg who had had viral loads <50 copies/mL for  $\geq 6$  months. The drug was well tolerated, and all of the 24 participants in the study had viral loads <50 copies/mL at Week 24.<sup>9</sup>

### Use of Biktarvy in Children Aged 6 Years to <12 Years

Studies of the adult dosage formulation of Biktarvy are underway in this age group.

## References

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2. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) [package insert]. Food and Drug Administration. 2018. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/210251s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf).
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## Dolutegravir (DTG, Tivicay) (Last updated May 22, 2018; last reviewed May 22, 2018)

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

### Formulations

**Tablets:** 10 mg, 25 mg, and 50 mg

**Fixed-Dose Combination Tablets:**

- [Triumeq] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg
- [Juluca] Dolutegravir 50 mg plus rilpivirine 25 mg

### Dosing Recommendations

#### Neonate/Infant Dose:

- Not approved for use in neonates/infants

#### Pediatric Dose (Weighing <30 kg):

- Not approved for children weighing <30 kg
- Clinical trials in children with HIV weighing <30 kg are under way (see text).

#### Pediatric Dose (Weighing ≥30 kg to <40 kg)

Body weight	Dose <sup>a</sup> (mg/day)	Dosing Frequency	Tablet Size (mg)
30 kg to <40 kg	35	Once daily	One 10-mg tablet plus one 25-mg tablet

<sup>a</sup> These doses are for children who are treatment-naïve or treatment-experienced (but integrase strand transfer inhibitor [INSTI]-naïve) and who are not being treated with UGT1A1/CYP3A inducers.

**Note:** Dolutegravir 10-mg and 25-mg tablets may be available in retail pharmacies. If dolutegravir 10-mg or 25-mg tablets must be ordered, have the pharmacy contact their drug wholesaler and tell the drug wholesaler to order directly from the GlaxoSmithKline (GSK) distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

### 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
- Hypersensitivity reactions, including rash, constitutional symptoms, and organ dysfunction (including liver injury) have been reported rarely.

### Special Instructions

- May be taken without regard to meals
- 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-, 25-, 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 semi-solid food or liquid, all of which should be consumed **immediately**.<sup>1</sup>
- The efficacy of 50-mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).
- When using fixed-dose combination (FDC) tablets, see other sections of the Drug Appendix for special instructions and additional information about the individual components of the FDC.

### Child and Adolescent (Weighing $\geq 40$ kg) and Adult Dose

Population	Recommended Dose
Treatment-naive or treatment-experienced/INSTI-naive	50 mg once daily
Treatment-naive or treatment-experienced/INSTI-naive when co-administered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with any INSTI-associated resistance substitutions or clinically suspected INSTI resistance <sup>a</sup>	50 mg twice daily

<sup>a</sup> Combinations that do not include metabolic inducers should be considered where possible.

### [Triumeq] Abacavir plus Dolutegravir plus Lamivudine

*Pediatric (Weighing  $\geq 40$  kg) and Adult Dose:*

- 1 tablet once daily
- For use in patients who are antiretroviral (ARV) treatment-naive or treatment-experienced (but INSTI-naive) and not being treated with UGT1A1/CYP3A inducers
- See [Abacavir](#) section for special instructions about testing for abacavir hypersensitivity.

### [Juluca] Dolutegravir plus Rilpivirine

*Adult Dose:*

- 1 tablet once daily with a meal as a complete regimen to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) on a stable ARV regimen for  $\geq 6$  months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Juluca.
- Not approved for children or adolescents. See Simplification of Treatment section below.

## Metabolism/Elimination

- UGT1A1 and cytochrome P450 (CYP) 3A substrate. **Drugs that induce these enzymes and transporters may decrease plasma concentrations of dolutegravir.**

### Dolutegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Because of lack of data, dolutegravir is not recommended in patients with severe hepatic impairment.
- Dolutegravir decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.

### Dolutegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is required in INSTI-naive patients with mild, moderate, or severe renal impairment or in INSTI-experienced patients with mild or moderate renal impairment.
- Use dolutegravir with caution in INSTI-experienced patients with severe renal impairment (creatinine clearance  $< 30$  mL/min) because dolutegravir concentrations will be decreased (the cause of this decrease is unknown).

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

- **Metabolism:** Dolutegravir is a UGT1A1 and cytochrome P450 (CYP) 3A substrate and may require dose adjustments when administered with UGT1A1 or CYP3A-modulating medications. Because etravirine significantly reduces plasma concentrations of dolutegravir, dolutegravir should not be administered with etravirine without co-administration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir, which counteract this effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data.
- **Atazanavir is an inhibitor of UGT1A1. In a recent pharmacologic survey of adult patients receiving**



dolutegravir, patients who also received atazanavir had two- to four-fold higher plasma dolutegravir concentrations than those receiving other antiretroviral (ARV) drugs.<sup>2</sup>

- Before dolutegravir is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.

### Major Toxicities

- *More common:* Insomnia and headache.
- *Less common (more severe):* Hypersensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction. Neuropsychiatric symptoms, especially in patients with a history of psychiatric illness. Multiple post-marketing reports note neuropsychiatric adverse effects (AEs) following initiation of dolutegravir-based therapy in adults.<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 presenting with advanced disease and initiating treatment with integrase inhibitors, particularly dolutegravir.<sup>5,6</sup> This phenomenon is presumed to be linked to the rapid decline in HIV-1 RNA observed with integrase inhibitor therapy.
- *Rare:* Hepatotoxicity. Two cases of presumed drug-induced liver injury, one requiring liver transplantation, have been reported.<sup>7,8</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 integrase strand transfer inhibitor (INSTI) mutations.

The efficacy of dolutegravir 50 mg twice daily is reduced in patients with INSTI-resistance Q148 substitution plus two or more additional INSTI-resistance mutations.

### Pediatric Use

#### Approval

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other ARV drugs for children weighing  $\geq 30$  kg and who are treatment-naive or treatment-experienced but INSTI-naive.<sup>9</sup>

The combination tablet abacavir/dolutegravir/lamivudine (Triumeq) is approved for adolescents weighing  $>40$  kg.<sup>10</sup> The combination tablet dolutegravir/rilpivirine (Juluca) is not approved for use in children or adolescents at the time of this review.<sup>11</sup>

### Efficacy and Pharmacokinetics

#### Aged $\geq 12$ years and Weighing $\geq 40$ kg

IMPAACT P1093 is an ongoing open-label trial of dolutegravir in children with HIV. FDA approval of dolutegravir for use in children weighing as low as 40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.<sup>12</sup> Intensive pharmacokinetic (PK) evaluations were performed on the first 10 participants, nine of whom weighed  $\geq 40$  kg and received dolutegravir 50 mg and one of whom weighed 37 kg and received dolutegravir 35 mg. These doses resulted in exposures comparable to those seen in adults receiving 50 mg once daily. Nine of 10 participants achieved HIV RNA concentration  $<400$  copies/mL at Week 4 (optimal background therapy was added 5–10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% of participants had achieved HIV RNA concentration  $<50$  copies/mL. No safety or tolerability concerns were identified. By Week 144, 39% and 30% of participants had achieved HIV RNA concentrations  $<400$  copies/mL and  $<50$  copies/mL, respectively. All who experienced virologic failure were nonadherent.

Additional long-term safety and efficacy data for this age group comes from a French, retrospective,

multicenter cohort study that evaluated 50 adolescents who initiated dolutegravir-based antiretroviral therapy (ART). Of 17 adolescents who were virologically suppressed at the time of dolutegravir-based treatment, 14 (82%) maintained suppression and three had transient viral rebound prior to re-achieving plasma viral load <50 copies/mL. Of the 33 viremic adolescents initiating dolutegravir, 19 (58%) achieved sustained virologic success. Overall, 66% achieved sustained virologic suppression and 78% had undetectable plasma viral load by the last study visit. Adolescents with virologic failure were more likely to be from sub-Saharan Africa and had more frequently detectable viremia in the 6 months prior to dolutegravir initiation. No resistance mutations emerged in patients with virologic failure, and only one patient discontinued dolutegravir-based treatment because of a significant AE (dizziness and sleep disturbance).<sup>13</sup>

#### **Aged ≥6 to <12 Years and Weighing ≥30 kg to <40 kg**

In addition, a younger cohort of children aged ≥6 to <12 years are undergoing PK and longer-term follow-up in IMPAACT P1093, with those weighing ≥30 kg to <40 kg receiving the 35-mg dose and those weighing ≥40 kg receiving the 50-mg dose. At 48 weeks, data from 23 participants demonstrated a favorable safety profile, adequate PK, and virologic efficacy, with HIV RNA concentrations of <50 copies/mL achieved in 74% (17/23) of participants.<sup>12,14</sup> This has led to FDA approval of the lower-strength tablets for children with HIV as young as age 6 years and weighing as low as 30 kg.

#### **Aged ≥6 Years, Weighing ≥15 kg to <20 kg or ≥20 kg to <30 kg**

The European Medicines Agency (EMA) approved the lower-strength tablets for children aged ≥6 years and weighing ≥15 kg based on population PK modelling and simulation analyses.<sup>15</sup> The EMA approved doses of 20 mg for children weighing 15 kg to <20 kg and 25 mg doses for those weighing 20 kg to <30 kg. Because the available PK data in these weight bands were minimal and the observed C<sub>trough</sub> concentrations were lower than expected, the FDA did not approve dosing for children weighing <30 kg. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) agrees with the FDA decision and does not recommend use of dolutegravir in this population at this time.

### **Pharmacokinetics of Dolutegravir in Adult and Pediatric Studies (P1093)**

<b>Population of Study</b>	<b>Weight (kg)</b>	<b>Dose (mg/day)</b>	<b>Tablet Size (mg)</b>	<b>Dosing Frequency</b>	<b>Dose for Lowest Weight in Weight Band (mg/kg)</b>	<b>Trough Plasma Concentration<sup>a</sup> mcg/mL<sup>b</sup></b>
<b>Adults with Prior INSTI Treatment</b>	>40	100	50	Twice daily	2.5	2.12 (47)
<b>Adults without Prior INSTI Treatment</b>	≥40	50	50	Once daily	1.25	1.11 (46)
<b>Children without Prior INSTI Treatment (N = 14)</b>	≥40	50	50	Once daily	1.25	0.99 (66)
<b>Children without Prior INSTI Treatment (N = 3)</b>	30 to <40	35	10 plus 25	Once daily	1.17	1.33 (93)
<b>Children without Prior INSTI Treatment (N = 4)</b>	20 to <30	25	25	Once daily	1.25	0.51 (44)

<sup>a</sup> Sources:

Dolutegravir [package insert]. Food and Drug Administration. 2016. Available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/204790Orig1s008lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf)

Food and Drug Administration. Tivicay (dolutegravir) clinical pharmacology review. 2016. Available at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM511918.pdf>

<sup>b</sup> Geometric mean (percent coefficient of variation)

**Note:** Recommendations for 100 mg/day are for adults with documented INSTI-resistance mutations using 50 mg twice daily (see product label or text above).

### ***Aged <6 Years and Not Able to Swallow Tablets***

IMPAACT P1093 is also investigating an oral pediatric granule formulation and a dispersible tablet for use in patients aged as young as 4 weeks. Data were recently reported from a cohort of patients aged >2 to <6 years receiving dolutegravir granules. Ten patients with median age of 4 years (range: 2–5 years) received approximately 0.8 mg/kg dolutegravir once daily; background regimens were optimized based on PK assessments that were completed after 5 to 10 days. The geometric mean area under the curve after 24 hours (AUC<sub>24h</sub>) was 44.7 mg\*hour/L and concentration after 24 hours (C<sub>24h</sub>) was 0.51 mg/L. Although the AUC<sub>24h</sub> target was achieved, the mean C<sub>24h</sub> was below the target value for this parameter. HIV-1 RNA levels were <400 copies/mL in 8 out of 10 participants at 4 weeks of treatment. Dolutegravir granules were well-tolerated in this age group and these data provide the basis for evaluating a 5-mg dispersible tablet.<sup>16</sup> The manufacturer of dolutegravir does not plan to produce the oral pediatric granule formulation.

### ***Simplification of Treatment***

Two recently reported trials (SWORD-1 and SWORD-2) in adults supported approval of a dolutegravir 50-mg and a rilpivirine 25-mg fixed-dose combination tablet (Juluca) as a complete regimen for treatment simplification or maintenance therapy in selected patients. The two identical SWORD trials enrolled 1,024 patients with suppressed viral replication who had been on stable ART for at least 6 months and had no history of treatment failure or evidence of resistance mutations. The participants were randomized to receive either dolutegravir/rilpivirine or a continuation of their suppressive ARV regimen. After 48 weeks of treatment, 95% of patients in both arms maintained HIV RNA <50 copies/mL.<sup>17</sup> More AEs were reported and led to discontinuation in the dolutegravir/rilpivirine arm. In a subgroup of SWORD study patients whose original ARV regimen contained tenofovir disoproxil fumarate, small but statistically significant increases in hip and spine bone mineral density were observed.<sup>18</sup> Although dolutegravir/rilpivirine (Juluca) is not approved for use in adolescents, the doses of both dolutegravir and rilpivirine in Juluca are approved for use in adolescents as single drugs. The Panel usually endorses adult formulations for use in adolescents, and this product may be appropriate for selected 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** use of Juluca for adolescents and children until more data are available.

### ***Crushing Tablets for Administration***

In patients who have difficulty swallowing whole tablets, 10-, 25-, 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 10-, 25-, and 50-mg 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 10-, 25-, and 50-mg tablets in water. In healthy adults, crushed tablets resulted in slightly higher exposures.<sup>19</sup>

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## Elvitegravir (EVG) (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

**Tablet:** Discontinued by the manufacturer. Only available in fixed-dose combination tablets.

#### Fixed-Dose Combination Tablets:

- [*Genvoya*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide (TAF) 10 mg
- [*Stribild*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir disoproxil (TDF) 300 mg

### Dosing Recommendations

#### [*Genvoya*] Elvitegravir plus Cobicistat plus Emtricitabine plus TAF

##### *Pediatric (Weighing <25 kg) Dose:*

- No data on appropriate dose of elvitegravir in *Genvoya* for children weighing <25 kg

##### *Child and Adolescent (Weighing ≥25 kg; Any Sexual Maturity Rating [SMR]) and Adult Dose:*

- One tablet once daily

#### [*Stribild*] Elvitegravir plus Cobicistat plus Emtricitabine plus TDF

##### *Pediatric (Weighing <35 kg) Dose:*

- No data on appropriate dose of elvitegravir in *Stribild* for children weighing <35 kg

##### *Adolescent (Weighing ≥35 kg and SMR 4 or 5) and Adult Dose:*

- One tablet once daily

**Note:** *Stribild* and *Genvoya* are Food and Drug Administration approved for use in ARV treatment-naïve patients or to replace the current ARV regimen in patients who are virologically suppressed (HIV-1 RNA <50 copies/mL) on at stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of *Genvoya* or *Stribild*.

### Selected Adverse Events

#### Elvitegravir-Associated Adverse Events:

- Diarrhea

#### *Stribild*-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

#### *TDF*-Specific Adverse Events:

- Renal insufficiency
- Decreased bone mineral density
- Flatulence

#### *Cobicistat*-Specific Adverse Events:

- Alteration in tubular secretion of creatinine

#### *Genvoya*-Associated Adverse Events:

- Nausea
- Diarrhea
- Fatigue
- Headache

#### *TAF*-Associated Adverse Events:

- Increased low-density lipoprotein-cholesterol and total cholesterol

#### *Cobicistat*-Associated Adverse Events:

- Alteration in tubular secretion of creatinine

### Special Instructions

- Administer with food.
- 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 at risk of renal impairment, also monitor serum phosphate. Patients with an increase in serum creatinine  $>0.4$  mg/dL should be closely monitored for renal safety.

- Screen patients for hepatitis B virus (HBV) infection before using emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF are discontinued; therefore, monitor hepatic function for several months after therapy with emtricitabine, TDF, or TAF is stopped.
- Neither Stribild nor Genvoya is recommended for use with other antiretroviral (ARV) drugs.

### **Metabolism/Elimination**

- Elvitegravir is metabolized by cytochrome P (CYP) 450 3A4 and is a modest inducer of CYP2C9.
- Elvitegravir should only be used with the pharmacokinetic enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to the [TDF](#) and [TAF](#) sections in the guidelines for further details.
- 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 because dose adjustments required for emtricitabine and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl  $<30$  mL/min.
- Neither Stribild nor Genvoya should be used in patients with severe hepatic impairment.

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

- *Metabolism:* Stribild and Genvoya contain elvitegravir and cobicistat. Elvitegravir is metabolized predominantly by cytochrome P (CYP) 450 3A4, secondarily by uridine diphosphate glucuronosyltransferase (UGT) 1A1/3, and by oxidative metabolism pathways. Elvitegravir is a modest inducer of CYP2C9. Cobicistat is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits the adenosine triphosphate-dependent transporters BCRP and P-glycoprotein and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. There is potential for multiple drug interactions when using both elvitegravir and cobicistat.
- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir disoproxil fumarate (TDF) or emtricitabine. Concomitant use of nephrotoxic drugs should be avoided when using Stribild.

- **Absorption:** Elvitegravir plasma concentrations are lower with concurrent administration of antacids because of the formation of complexes in the gastrointestinal tract and not because of changes in gastric pH. Separate administration of Genvoya and antacids by at least 2 (preferably 4) hours. Absorption of integrase inhibitors, including elvitegravir, is decreased by chelation by high concentrations of divalent cations like iron, so administration of Genvoya should be separated from administration of iron supplements or multivitamins containing iron, by at least 4 hours.
- **Protease inhibitors:** Neither Stribild nor Genvoya should be administered concurrently with products or regimens containing ritonavir due to the similar effects of cobicistat and ritonavir on CYP3A4 metabolism.
- Neither Stribild nor Genvoya is recommended for use with other antiretroviral (ARV) drugs.

### Major Toxicities

- **More common:** Nausea, diarrhea, and flatulence.
- **Less common (more severe):** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with nucleoside reverse transcriptase inhibitors, including TDF and emtricitabine. TDF caused bone toxicity (osteomalacia and reduced bone mineral density [BMD]) in animals when given in high doses. Decreases in BMD have been reported in both adults and children taking TDF; the clinical significance of these changes is not yet known. Evidence of renal toxicity has been observed **in patients taking** TDF, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate. 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 treated with Stribild.

### Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of [updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation. There is phenotypic cross-resistance between elvitegravir and raltegravir.<sup>1</sup>

### Pediatric Use

#### Approval

Elvitegravir was Food and Drug Administration (FDA)-approved in 2014 as a tablet (Vitekta) for use in adults in combination with a protease inhibitor plus ritonavir. **The drug manufacturer removed Vitekta from the market in February 2017 and elvitegravir is no longer available as a single-agent ARV.**

Elvitegravir was FDA-approved in 2012 for use in adults as part of the fixed-dose combination product Stribild, which contains elvitegravir, cobicistat, emtricitabine, and TDF. Stribild is FDA-approved for use in children aged **≥12 years and weighing ≥35 kg.**<sup>2,3</sup>

Genvoya, a fixed-dose combination product which contains elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (TAF), was FDA-approved for use in children aged ≥12 years and weighing ≥35 kg **in November 2015. In September 2017, Genvoya was FDA-approved for use in children aged >6 years and weighing >25 kg.**<sup>4</sup>

#### Efficacy in Clinical Trials

A combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be non-inferior to a regimen of efavirenz/emtricitabine/TDF<sup>5</sup> and non-inferior to a regimen of atazanavir/ritonavir (ATV/r) with emtricitabine/TDF in adults at 144 weeks of treatment.<sup>6</sup> In two studies, 1,733 adults were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TAF. After 48 weeks, those receiving elvitegravir/cobicistat/emtricitabine/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL;  $P < 0.0001$ ), significantly less proteinuria (median percent change

-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%;  $P < 0.0001$ ).<sup>7</sup>

### Formulations

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Elvitegravir must be used in the fixed-dose combination products Stribild<sup>3</sup> or Genvoya,<sup>4</sup> which contain cobicistat (see below). Cobicistat itself does not have ARV activity, but is a CYP3A4 inhibitor that acts as a pharmacokinetic (PK) enhancer, similar to ritonavir.<sup>8</sup>

Stribild is FDA-approved as a complete antiretroviral therapy (ART) regimen in ARV-naive adults with HIV-1 aged  $\geq 18$  years or to replace the current ART regimen in those who are virologically suppressed (HIV-1 RNA  $< 50$  copies/mL) on a stable ART regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Stribild.<sup>3</sup> Trials have shown that Stribild is non-inferior to regimens of emtricitabine combined with TDF plus ATV/r,<sup>9,10</sup> or emtricitabine plus TDF plus efavirenz.<sup>11,12</sup> Cobicistat inhibits renal tubular secretion of creatinine, and serum creatinine will often increase soon after initiation of treatment with Stribild. Therefore, creatinine-based calculations of estimated glomerular filtration rate (GFR) will be altered, even though the actual GFR might be only minimally changed.<sup>13</sup> Adults who experience a confirmed increase in serum creatinine  $> 0.4$  mg/dL from baseline should be closely monitored for renal toxicity by following creatinine for further increases and urinalysis for evidence of proteinuria or glycosuria.<sup>3</sup> Careful periodic evaluation of renal function is warranted because Stribild contains TDF, which can be associated with renal toxicity. This nephrotoxicity may be more pronounced in patients with pre-existing renal disease.<sup>3</sup>

Genvoya is FDA-approved as a complete ART regimen in ARV-naive individuals with HIV-1 aged  $\geq 6$  years and weighing  $\geq 25$  kg or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA  $< 50$  copies/mL) on a stable ART regimen for at least 6 months, with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.<sup>4</sup> Because Genvoya contains TAF instead of TDF, Genvoya would be expected to have less bone and renal toxicity compared to Stribild. Two studies of adults have shown that Genvoya has diminished renal and bone toxicity when compared to Stribild. After 48 weeks of treatment, participants treated with Genvoya had significantly smaller increases in serum creatinine, less proteinuria, and smaller decreases in BMD at the spine and hip than participants treated with Stribild.<sup>7</sup>

### Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 years

Studies of the adult dosage formulation of Stribild used in children with HIV aged  $\geq 12$  years and weighing  $\geq 35$  kg have demonstrated PK, safety, and efficacy similar to that in adults through 24 weeks of study.<sup>3</sup> Studies of the adult dosage formulation of Genvoya in children with HIV aged  $\geq 12$  years and weighing  $\geq 35$  kg have shown safety comparable to that of adults,<sup>14</sup> and this formulation is FDA-approved for use in this age/weight group. Genvoya is preferable to Stribild for treatment of youth with sexual maturity rating 1 to 3 because of the diminished renal and bone toxicity of Genvoya compared with Stribild.<sup>4</sup>

### Use of Elvitegravir as Genvoya in Children Aged 6 to $< 12$ years

Genvoya is approved by the FDA to treat children aged 6 to  $< 12$  years and weighing  $\geq 25$  kg<sup>4</sup> based on a 24-week safety study in 23 children.<sup>15</sup> There were no study discontinuations due to medication toxicity, but at Week 24 the participants' CD4 T lymphocyte (CD4) cell counts had decreased by median of 130 cells/mm<sup>3</sup> (with a range of 472–266 cells/mm<sup>3</sup>), and CD4 percent decreased by a median of 2.1% (with a range of 8.4% to 5.9%). Stribild is not FDA-approved for use in children weighing  $< 25$  kg.

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## Raltegravir (RAL, Isentress) (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:** 400 mg (film-coated poloxamer tablet)

**HD Tablets:** 600 mg (film-coated poloxamer tablet)

**Chewable Tablets:** 100 mg (scored) and 25 mg

**Granules for Oral Suspension:** Single-use packet of 100 mg of raltegravir, suspended in 10 mL of water for final concentration of 10 mg/mL.

**Note:** Film-coated tablets, chewable tablets, and oral suspension **are not interchangeable**.

### Dosing Recommendations

See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12. Newborn Antiretroviral Dosing Recommendations](#) for prevention of perinatal transmission.

#### Neonate Dose:

Neonates  $\geq 37$  Weeks of Gestation (Weighing  $\geq 2$  kg):

- No dosing information is available for preterm or low birthweight infants.

#### Oral Suspension Dosing Table

Full-Term Neonates (Birth to 4 Weeks [28 Days] of Age):

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
<b>Birth to 1 Week: Once-Daily Dosing</b>	<b>Approximately 1.5 mg/kg/dose</b>
2 to <3	0.4 mL (4 mg) once daily
3 to <4	0.5 mL (5 mg) once daily
4 to <5	0.7 mL (7 mg) once daily
<b>1–4 Weeks: Twice-Daily Dosing</b>	<b>Approximately 3 mg/kg/dose</b>
2 to <3	0.8 mL (8 mg) twice daily
3 to <4	1 mL (10 mg) twice daily
4 to <5	1.5 mL (15 mg) twice daily

**Note:** If the mother has taken raltegravir 2 to 24 hours prior to delivery, the neonate's first dose should be delayed until 24 to 48 hours after birth.

**Note:** Metabolism by uridine diphosphate glucotransferase (UGT1A1) is low at birth and increases rapidly over the next 4 to 6 weeks of life.

### Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache, dizziness, fatigue
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

### Special Instructions

- Can be given without regard to food.
- Co-administration or staggered administration of aluminum- and magnesium-containing antacids **is not recommended** with any raltegravir formulations.
- Significant drug interactions are more likely to occur when the raltegravir HD formulation is used once daily. **The following drugs should not be co-administered:** 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.**
- 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 preparations.
- Chewable tablets should be stored in the

## Infant and Pediatric Dose

### Oral Suspension Dosing Table<sup>a</sup>

Children Aged  $\geq 4$  Weeks and Weighing  $\geq 3$  kg to  $< 20$  kg:

Body Weight (kg)	Volume (Dose) of Suspension to be Administered
3 to $< 4$	2.5 mL (25 mg) twice daily
4 to $< 6$	3 mL (30 mg) twice daily
6 to $< 8$	4 mL (40 mg) twice daily
8 to $< 11$	6 mL (60 mg) twice daily
11 to $< 14$	8 mL (80 mg) twice daily
14 to $< 20$	10 mL (100 mg) twice daily

<sup>a</sup> The weight-based dosing recommendation for the oral suspension is based on approximately 6 mg/kg/dose twice daily.

**Note:** Maximum dose of oral suspension is 10 mL (100 mg) twice daily.

**Note:** For children weighing 11 kg to 20 kg, either oral suspension or chewable tablets can be used.

### Pediatric Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

Children Weighing  $\geq 11$  kg:

- $< 25$  kg: Chewable tablets twice daily. See table below for chewable tablet dose.
- $\geq 25$  kg: 400-mg film-coated tablet twice daily **or** chewable tablets twice daily. See table below for chewable tablet dose.

**Child and Adolescent Weighing  $\geq 50$  kg (HD), see Pediatric Use, Approval:**

- 1200 mg (two 600 mg HD) once daily
- For treatment-naïve or virologically suppressed patients on an initial regimen of 400 mg twice daily.

Body Weight (kg)	Dose	Number of Chewable Tablets
11 to $< 14$	75 mg twice daily	3 X 25 mg twice daily
14 to $< 20$	100 mg twice daily	1 X 100 mg twice daily
20 to $< 28$	150 mg twice daily	1.5 X 100 mg <sup>b</sup> twice daily
28 to $< 40$	200 mg twice daily	2 X 100 mg twice daily
$\geq 40$	300 mg twice daily	3 X 100 mg twice daily

<sup>a</sup> The weight-based dose recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

<sup>b</sup> The 100-mg chewable tablet can be divided into equal halves.

**Note:** Maximum dose of chewable tablets is 300 mg twice daily.

original package with desiccant to protect them from moisture.

- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- Oral suspension is provided in kits that include mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions are provided in the Instructions for Use document. Each foil packet is single-use and contains 100 mg of raltegravir, which will be suspended in 10 mL of water for a final concentration of 10 mg/mL. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension.
- Do not shake the oral suspension. Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document.

## Metabolism/Elimination

- UGT1A1-mediated glucuronidation

### Raltegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary for standard-dose raltegravir in patients with mild-to-moderate hepatic insufficiency. No dosing studies of raltegravir HD have been done in patients with hepatic impairment. Therefore, administration of raltegravir HD is **not recommended** in patients with hepatic impairment. The effect of severe hepatic impairment on raltegravir pharmacokinetics has not been studied.

### Raltegravir Dosing in Patients with Renal Impairment:

- No dose adjustment necessary in patients with any degree of renal impairment.

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

- **Metabolism:** The major route of raltegravir elimination is mediated through glucuronidation by uridine diphosphate glucotransferase (UGT1A1).
- Inducers of UGT1A1, such as rifampin and tipranavir, may result in reduced plasma concentrations of raltegravir. Inhibitors of UGT1A1, such as atazanavir, may increase plasma concentrations of raltegravir. No dosing modifications are recommended when raltegravir is co-administered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r) **(except with HD tablets-see note below)**.
- **In adults, an increased** dose of raltegravir is recommended when it is co-administered with rifampin. For adults receiving rifampin, the recommended raltegravir dose is 800 mg twice daily. **Do not co-administer** rifampin with once-daily raltegravir HD tablets. The appropriate dose adjustment is not known in children and is currently being studied in IMPAACT P1101.
- **Aluminum- and magnesium-containing antacids may reduce raltegravir plasma concentrations and should not be co-administered.**
- **Significant drug interactions may be more likely to occur with raltegravir HD once daily.  $C_{trough}$  concentrations in adults are approximately 30% lower with raltegravir HD 1200 mg once daily than with raltegravir 400 mg twice daily. A lower  $C_{trough}$  increases the potential for clinically significant drug interactions with interfering drugs that decrease raltegravir exposure and further lower  $C_{trough}$ . In addition to aluminum- and magnesium-containing antacids, the following drugs should not be co-administered with raltegravir: calcium carbonate, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug metabolizing enzymes on raltegravir is unknown; co-administration with phenytoin, phenobarbital, and carbamazepine is not recommended.**
- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with raltegravir.

## **Major Toxicities**

- **More common:** Nausea, headache, dizziness, diarrhea, fatigue, itching, and 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 Grade from baseline for laboratory abnormalities of** aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than are patients who are not co-infected.
- **Rare:** Moderate to severe increase in creatine phosphokinase. Use raltegravir with caution in patients receiving medications associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with prior history. Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis. Thrombocytopenia. Cerebellar ataxia. Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications.

## **Resistance**

The International 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*

Raltegravir is an integrase strand transfer inhibitor that is Food and Drug Administration (FDA)-approved for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV-1 infection in **pediatric patients weighing  $\geq 2$  kg**. Current pediatric FDA approval and dose recommendations are based on

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evaluations in 122 patients aged  $\geq 4$  weeks to 18 years enrolled in IMPAACT P1066 and 42 neonates treated for  $\leq 6$  weeks starting from birth and followed for a total of 24 weeks in IMPAACT P1110.<sup>1</sup>

Overall, raltegravir has a favorable safety profile and is available in formulations suitable for administration to neonates, infants, and young children.

The FDA has approved raltegravir HD, which allows once daily dosing, for use in children and adolescents  $\geq 40$  kg, but the Panel recommends using it in children  $\geq 50$  kg since there are no clinical data on raltegravir HD once-daily dosing in children or adolescents  $< 50$  kg.

#### Efficacy in Clinical Trials (Adults and Children):

- Raltegravir has been evaluated in adults in three large randomized clinical trials: STARTMRK, SPRING-2, and ACTG A5257. In STARTMRK, a raltegravir-containing regimen was compared to an efavirenz-containing regimen. At 48 weeks, raltegravir was non-inferior to efavirenz. However, more patients discontinued efavirenz during the longer follow-up periods of 4 and 5 years, and raltegravir was found to be superior.<sup>2-4</sup> SPRING-2 compared raltegravir to dolutegravir and demonstrated non-inferiority of dolutegravir.<sup>5</sup> ACTG A5257 compared raltegravir to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but raltegravir had better tolerability.<sup>6</sup>
- Raltegravir has been studied in infants, children, and adolescents in IMPAACT P1066, an open-label trial that evaluated pharmacokinetics (PK), safety, tolerability, and efficacy. In 96 participants aged 2 years to 18 years who were mostly treatment-experienced, 79.1% of the patients achieved a favorable viral load response (i.e., HIV viral load  $< 400$  copies/mL or  $\geq 1$  log<sub>10</sub> decline in viral load) while receiving the currently recommended dose of raltegravir. Infants and toddlers aged  $\geq 4$  weeks to  $< 2$  years were also enrolled in IMPAACT P1066 and received treatment with raltegravir oral suspension. At Weeks 24 and 48, 61% of the participants (14/23 infants and toddlers) had an HIV viral load  $< 400$  copies/mL.<sup>7-9</sup>
- The ONCEMRK study compared raltegravir 1200 mg once daily (taken as two 600-mg HD tablets) to raltegravir 400 mg twice daily in treatment-naïve adults. Once-daily dosing of raltegravir 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 raltegravir regimen. While the HD tablets are FDA-approved for children weighing  $\geq 40$  kg, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend using HD tablets in children weighing  $< 50$  kg (see below).

#### ***Efficacy and Pharmacokinetics of Once-Daily Dosing (Children and Adults)***

Raltegravir PK exhibit considerable intrasubject and intersubject variability.<sup>10,11</sup> Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naïve patients with HIV were randomized to receive raltegravir 800 mg once daily versus raltegravir 400 mg twice daily (BID). After 48 weeks of treatment, the percentage of patients achieving 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 were at the greatest risk of treatment failure.<sup>10,11</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 raltegravir trough plasma concentrations above 45 nM is important for efficacy.<sup>10,11</sup>

Higher, once-daily dosing with raltegravir 1200 mg was found to be as effective as 400 mg twice daily. In the ONCEMRK study, 797 treatment-naïve adults were randomized to receive either 1200 mg of raltegravir once daily (taken as two 600-mg tablets) or 400 mg of raltegravir twice daily plus tenofovir disoproxil fumarate plus emtricitabine. After 48 weeks, 89% of participants on the once-daily dose versus 88% of participants on the twice-daily dose reached viral loads of  $< 40$  copies. There was no difference in discontinuation rates due to side effects.<sup>12</sup> In May 2017, once-daily dosing of raltegravir 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 raltegravir regimen. The use of once-daily HD tablets has not been studied in pediatric patients.

Population PK modeling and simulations of once daily raltegravir HD tablets predict similar drug exposures to those observed in adult patients in ONCEMRK.<sup>1,13</sup>

No significant differences in PK are anticipated with the administration of two 600-mg HD tablets (1200 mg) given once daily compared to three 400-mg (1200 mg) tablets given once daily. In adults enrolled in ONCEMRK, the  $C_{\text{trough}}$  concentrations were approximately 30% lower in participants taking once-daily raltegravir HD tablets than in those taking raltegravir 400 mg twice daily. Because of this, the potential for significant drug interactions is greater with once daily dosing as interfering drugs that decrease drug exposure may further decrease  $C_{\text{trough}}$ .  $C_{\text{max}}$  is approximately six times higher with raltegravir 1200 mg once daily when compared to raltegravir 400 mg twice daily, with a two-fold higher area under the curve (AUC).

While modeling and simulations for pediatric patients may indicate that PK targets are met using the once-daily raltegravir 1200 mg regimen, safety cannot be extrapolated for children weighing <50 kg. There were six children in IMPAACT P1066 who had similar drug exposures as those observed in ONCEMRK, but all weighed >50 kg. Potential dose-related central nervous system toxicities, such as insomnia or hyperactivity, might occur with very high raltegravir concentrations in children.<sup>1</sup> The Panel recommendations differ from those of the FDA because there are no clinical data on once-daily raltegravir HD tablet dosing in children or adolescents weighing <50 kg. While the FDA has approved once-daily raltegravir HD tablets for use in children weighing  $\geq 40$  kg, the Panel recommends that once-daily raltegravir HD tablets only be used in children and adolescents weighing  $\geq 50$  kg.

### Efficacy and Pharmacokinetics in Children

IMPAACT P1066 was conducted to evaluate the PK, safety, and efficacy of raltegravir in children aged 4 weeks to 18 years. Enrollment by cohort and PK parameters are summarized in Tables A and B.<sup>8,9</sup>

**Table A. Summary of IMPAACT P1066 Cohorts and Participation<sup>8,9</sup>**

Age	Cohort	Formulation	Participants Receiving the Final Recommended Dose
12 Years to <19 Years	I	Film-coated tablet	N = 59
6 Years to <12 Years	IIA	Film-coated tablet	N = 4
6 Years to <12 Years	IIB	Chewable tablet	N = 13
2 Years to <6 Years	III	Chewable tablet	N = 20
6 Months to <2 Years	IV	Oral suspension	N = 14
4 Weeks to <6 Months	V	Oral suspension	N = 12

**Table B. Summary of IMPAACT P1066 PK Results by Cohort<sup>8,9</sup>**

Age	Cohort	Formulation	Intensive PK	Mean Dose mg/kg	GM (CV%) <sup>a</sup> AUC <sub>0-12h</sub> $\mu\text{Mxh}$	GM (CV%) <sup>b</sup> C <sub>12h</sub> nM
12 Years to <19 Years	I	Film-coated tablet	N = 11	9.3	15.7 (98)	333 (78)
6 Years to <12 Years	IIA	Film-coated tablet	N = 11	13.5	15.8 (120)	246 (221)
6 Years to <12 Years	IIB	Chewable tablet	N = 10	6.5	22.6 (34)	130 (88)
2 Years to <6 Years	III	Chewable tablet	N = 12	6.2	18.0 (59)	71 (55)
6 Months to <2 Years	IV	Oral suspension	N = 8	5.9	19.8 (34)	108 (52)
4 Weeks to <6 Months	V	Oral suspension	N = 11	5.7	22.3 (40)	117 (68)

<sup>a</sup> PK targets for Cohorts I–III: AUC<sub>0-12h</sub> 14–25  $\mu\text{Mxh}$ ; C<sub>12h</sub> nM  $\geq 33$  nM

<sup>b</sup> PK targets for Cohorts IV–V: AUC<sub>0-12h</sub> 14–45  $\mu\text{Mxh}$ ; C<sub>12h</sub> nM  $\geq 75$  nM

**Key to Acronyms:** AUC = area under the curve; C<sub>12h</sub> = concentration at 12 hours (trough); CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic

## *Children Aged 2 to 18 Years*

IMPAACT P1066 was a Phase 1/2 open-label multicenter study that evaluated the PK profile, safety, tolerability, and efficacy of various formulations of raltegravir in antiretroviral treatment (ART)-experienced children and adolescents with HIV aged 2 years to 18 years in combination with an optimized background ART regimen.<sup>9,14</sup> Subjects received either the 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 6 mg/kg twice daily (aged 2 years to <12 years). In IMPAACT P1066, the initial dose-finding stage included intensive PK evaluation in various age cohorts (Cohort I: aged 12 years to <19 years; Cohort II: 6 years to <12 years, Cohort III: 2 years to <6 years). Dose selection was based on achieving target PK parameters similar to those seen in adults: PK targets were geometric mean (GM)  $AUC_{0-12h}$  of 14 to 25  $\mu M \cdot hr$  and GM 12-hour concentration ( $C_{12h}$ )  $> 33$  nM. Additional subjects were then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. A total of 126 treatment-experienced participants were enrolled, with 96 receiving the final recommended dose of raltegravir. Only treatment-experienced patients were eligible to enroll, and the optimized regimen was determined by the site investigators. Adolescents tended to be more treatment-experienced and have more advanced disease than those in the younger cohorts. 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 (percent [%]) increase of 156 cells/mm<sup>3</sup> (4.6%).<sup>9</sup> Of 36 subjects who experienced virologic failure, development of drug resistance and/or poor adherence were contributing factors. Genotypic resistance data were available for 34 patients with virologic failure, and raltegravir-associated mutations were detected in 12/34 of those subjects. The frequency, type, and severity of adverse events (AEs) through Week 48 were comparable to those observed in adult studies. AEs were commonly reported, but there were few serious AEs considered to be drug-related. Observed AEs 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>9</sup> Overall, raltegravir administered as a film-coated tablet twice daily in subjects aged 6 to <19 years and as chewable tablets at a dose of approximately 6 mg/kg twice daily in subjects aged 2 to <12 years was well tolerated, with favorable virologic and immunologic responses.<sup>15</sup>

In 19 children and adolescents non-responders with multidrug-resistant virus in the HIV Spanish Cohort (CoRISe), had good virologic response and improved CD4 counts when raltegravir was included in an optimized regimen.<sup>7</sup> Additional experience from the French expanded access program in treatment-experienced adolescents supports the good virologic and immunologic results observed in IMPAACT P1066.<sup>16,17</sup>

## *Infants and Toddlers Aged at Least 4 Weeks to <2 Years*

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the granules for raltegravir oral suspension in combination with an optimized background regimen. All subjects had received prior ARV drugs as part of prevention of perinatal transmission and/or treatment of HIV, and 69% had baseline plasma HIV-1 RNA exceeding 100,000 copies/mL. PK targets for Cohorts IV and V were modified to GM  $AUC_{0-12h}$  of 14 to 45  $\mu M \cdot hr$  and GM 12-hour concentration ( $C_{12h}$ )  $\geq 75$  nM (33.3 ng/mL). These targets were modified so that greater than 90% of patients would be predicted to have  $C_{12h}$  above the 45 nM threshold. By Week 48, two subjects experienced AEs thought to be related to the study drug: one patient with a serious erythematous rash that resulted in permanent discontinuation of raltegravir, and one patient with immune reconstitution inflammatory syndrome. Virologic success, defined as  $\geq 1$  log<sub>10</sub> decline in HIV RNA or  $< 400$  copies/mL at 48 weeks, was achieved in more than 87% of subjects. At 48 weeks of follow-up, 45.5% of subjects had HIV RNA  $< 50$  copies/mL and mean CD4 cell count (percent [%]) increases of 527.6 cells/mm<sup>3</sup> (7.3%). There were four subjects in Cohort IV with virologic failure by Week 48 and one subject with a raltegravir-associated resistance mutation on genotype. Overall, the granules for oral suspension, at a dose of approximately 6 mg/kg twice daily, were well tolerated with good efficacy.<sup>8</sup>

### Neonates Aged <4 Weeks

Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for UGT and albumin binding sites.<sup>18</sup> Washout PK of raltegravir in neonates born to pregnant women with HIV was studied in IMPAACT P1097.<sup>19</sup> The neonatal plasma half-life was highly variable, ranging from 9.3 to 184 hours, suggesting potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of raltegravir.

IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates exposed to HIV and at risk of acquiring HIV-1 infection, with or without (i.e., raltegravir-naïve) *in utero* raltegravir exposure. Study design included two cohorts: Cohort 1 infants received two single raltegravir doses 1 week apart and Cohort 2 infants received daily raltegravir dosing for the first 6 weeks of life. PK data from Cohort 1 and from older infants and children were combined in a population PK model and simulations were used to select the following daily raltegravir dosing regimen for evaluation in raltegravir-naïve infants in Cohort 2: 1.5 mg/kg daily, starting within 48 hours of life through Day 7; 3 mg/kg twice daily on Days 8 to 28 of life; 6 mg/kg twice daily after 4 weeks of age.<sup>20,21</sup> Protocol exposure targets for each subject are AUC<sub>0-24hr</sub> 12 to 40 mg\*h/L, AUC<sub>0-12hr</sub> 6 to 20 mg\*h/L, C<sub>12hr</sub> or C<sub>24hr</sub> >33 ng/mL. Safety was assessed based on clinical and laboratory evaluations.<sup>19,22,23</sup> Twenty-six raltegravir-naïve infants were enrolled in Cohort 2. Evaluable PK results and safety data are available for 25 infants. Results for raltegravir-naïve infants enrolled in Cohort 2 are contained in the summary table below.

**Table C. IMPAACT P1110 Cohort 2 Intensive PK Results<sup>23</sup>**

PK Parameters				
	After Initial Dose: 1.5 mg/kg Once Daily (N = 25)		Days 15–18: 3.0 mg/kg Twice Daily (N = 24)	
	Geometric Mean (CV)	Target	Geometric Mean (CV)	Target
AUC (mg*h/L)	38.2 (38.4%)	Above: 11 Met: 13 Below: 0	14.3 (43.3%)	Above: 8 Met: 14 Below: 1
Trough (ng/mL)	948 (64.2%)	Above: 25 Below: 0	176 (93.8%)	Above: 22 Below: 1
C <sub>max</sub> (ng/mL)	2,350 (35.0%)	Above: 0 Below: 25	2,850 (41.9%)	Above: 0 Below: 24
T <sub>max</sub> (hrs)	5.4 (57.5%)	N/A	2.3 (67.1%)	N/A
T <sub>1/2</sub> (hrs)	15.8 (174.8%)	N/A	2.5 (33.5%)	N/A

**PK Targets:** AUC<sub>24</sub>, 12–40 mg\*h/L; AUC<sub>12</sub>, 6–20 mg\*h/L

**Trough Concentrations:** >33 ng/mL

**Key to Acronyms:** AUC = area under the curve; C<sub>max</sub> = maximum concentration; CV = coefficient of variation; PK = pharmacokinetic; T<sub>1/2</sub> = half-life; T<sub>max</sub> = time to reach maximum concentration

Daily raltegravir was safe and well tolerated during the first 6 weeks of life. **Infants were treated for up to ≤6 weeks from birth and followed for a total of 24 weeks.** All GM protocol exposure targets were met. In some infants, AUC<sub>0-24hr</sub> following initial dose was slightly above target range, but this is considered acceptable given the rapid increase in raltegravir metabolism over the first week of life. The PK targets and the safety guidelines were met for raltegravir-unexposed infants in Cohort 2 using the specified dosing regimen. **No drug-related clinical AEs were observed. Three laboratory adverse reactions were reported: Grade 4 transient neutropenia occurred in one infant receiving the zidovudine-containing regimen; two bilirubin elevations**



(one each, Grade 1 and Grade 2) were considered non-serious and did not require specific therapy.<sup>1</sup> The safety and PK data for daily dosing collected from IMPAACT P1110 are from raltegravir-naïve infants in Cohort 2; data collection from infants born to mothers who were receiving raltegravir is ongoing. However, the Panel believes that the FDA-approved dosing (including delaying the first dose for infants born to mothers who received raltegravir) is reasonable based on current data about clearance from premature and raltegravir-exposed infants.

### Formulations

The PK of raltegravir was compared in adult patients with HIV who swallowed intact, whole 400-mg tablets and patients who chewed the 400-mg film-coated tablets because of swallowing difficulties. Drug absorption was significantly higher in the group who chewed the tablets, although the palatability was rated as poor.<sup>24</sup> In adult volunteers, the PK of raltegravir 800 mg taken once daily by chewing was compared to two doses of raltegravir 400 mg taken every 12 hours by swallowing. Subjects taking raltegravir by chewing had significantly higher drug exposure and reduced PK variability than swallowing whole tablets as currently recommended.<sup>25</sup> According to the manufacturer, the film-coated tablets must be swallowed whole.

The raltegravir chewable tablet and oral suspension have higher oral bioavailability than the 400-mg film-coated tablet, based on a comparative study in healthy adult volunteers.<sup>26</sup> Compared with the raltegravir 400-mg tablet formulation, the 600-mg tablet has higher relative bioavailability.<sup>1</sup> Interpatient and inpatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.<sup>1,27</sup> Because of differences in the bioavailability of various formulations, the dosing recommendations differ and the formulations are not interchangeable. When prescribing raltegravir, clinicians should refer to the appropriate dosing table for the various formulations. While the raltegravir chewable tablets are not yet approved for use in children aged <2 years, a recent study has investigated whether these tablets may be dispersed and administered to younger children and infants.<sup>28</sup> An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including breastmilk. A follow-up evaluation of chewable tablets used as dispersible tablets in young children is planned.

Palatability was evaluated as part of IMPAACT P1066. Both chewable tablets and oral granules for suspension were thought to have acceptable palatability. Seventy-three percent of those surveyed reported no problems with chewable tablets; 82.6% reported no problems with administering the oral granules.<sup>8,9</sup>

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## Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

## Cobicistat (COBI, TYBOST) (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:** 150 mg

#### Fixed-Dose Combination Tablets:

- [Stribild] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir disoproxil fumarate (TDF) 300 mg
- [Genvoya] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide (TAF) 10 mg
- [Evotaz] Atazanavir 300 mg plus cobicistat 150 mg
- [Prezcobix] Darunavir 800 mg plus cobicistat 150 mg

### Dosing Recommendations

#### Cobicistat is a Pharmacokinetic (PK) Enhancer:

- The only use of cobicistat is as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and selected integrase inhibitors. Cobicistat **is not interchangeable** with ritonavir. See dosing information for [elvitegravir](#) and specific [PIs](#) that require cobicistat for boosting.

#### Pediatric Dosing

*Not Food and Drug Administration (FDA)-Approved for Use in Children Aged <18 Years:*

- Cobicistat alone (as Tybost)
- Evotaz
- Prezcobix
- Some members of the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV regard the above agents as potentially appropriate for use in select children aged <18 years and weighing  $\geq 35$  kg. An expert in pediatric HIV infection should be consulted.

*Not FDA-Approved for Use in Children Aged <6 Years or Weighing <25 kg:*

- Genvoya

*Not FDA-Approved for Use in Children Aged <12 years Weighing <35 kg:*

- Stribild

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

- Cobicistat 150 mg orally once daily as a component of Genvoya

### Selected Adverse Events

- When co-administered with TDF, cobicistat may be associated with higher risk of renal tubular adverse events than ritonavir.

### Special Instructions

- Cobicistat **is not interchangeable** with ritonavir.
- **Do not administer** cobicistat with ritonavir or with drugs containing cobicistat.
- Not recommended for use with more than one ARV drug that requires PK enhancement (e.g., elvitegravir in combination with a PI) because no data are available.
- Use with PIs other than atazanavir 300 mg or darunavir 800 mg administered once daily is not recommended because no data are available on other combinations or doses.
- Patients with a confirmed increase in serum creatinine  $>0.4$  mg/dL from baseline should be closely monitored for renal safety.
- When used in combination with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy (see [Table 15i](#)). In patients at risk of renal impairment, also monitor serum phosphate.
- When used in combination with other ARV drugs, see those specific sections of the appendix ([atazanavir](#), [darunavir](#), [elvitegravir](#), [TDF](#), [TAF](#)).

### Metabolism/Elimination

- Cytochrome P (CYP) 3A4 and CYP2D6 inhibitor

### Adolescent (Weighing $\geq 35$ kg and SMR 4 or 5)

#### Dose:

- Cobicistat 150 mg orally once daily as a component of Stribild

#### Adult (Aged $\geq 18$ Years) Dose:

- Cobicistat must be administered as:
  - The combination tablets Stribild or Genvoya, in which case it would not be dosed with any other antiretroviral (ARV) drugs; *or*
  - The tablet Tybost co-administered with atazanavir or darunavir at the doses listed in the table below and at the same time, in combination with other ARV drugs; *or*
  - Combination tablets with atazanavir (Evotaz) or darunavir (Prezcobix), with food, and in combination with other ARV drugs.

Cobicistat Dose	Co-Administered Agent Dose	Patient Population
150 mg orally once daily	As part of Stribild or Genvoya; no other ARV drugs needed	Treatment-naïve or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya
150 mg orally once daily	Atazanavir 300 mg (coformulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naïve or treatment-experienced
150 mg orally once daily	Darunavir 800 mg (coformulated as Prezcobix or given as a separate drug) orally once daily plus other ARV drugs	Treatment-naïve or treatment-experienced with no darunavir-associated resistance mutations

- P-glycoprotein and breast cancer resistance protein inhibitor

- Cobicistat inhibits renal tubular secretion of creatinine, increasing the serum creatinine concentration (and decreasing estimated glomerular filtration rate) without decreasing actual glomerular function.

#### Cobicistat Dosing in Patients with Renal Impairment:

- Stribild should not be initiated in patients with estimated creatinine clearance (CrCl)  $<70$  mL/min and should be discontinued in patients with estimated CrCl  $<50$  mL/min because dose adjustments required for emtricitabine and TDF cannot be achieved with a fixed-dose combination tablet.
- Genvoya should not be initiated in patients with estimated CrCl  $<30$  mL/min.
- Neither Stribild nor Genvoya should be used in patients with severe hepatic impairment.

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

- Metabolism:** Cobicistat is an inhibitor of cytochrome P (CYP) 3A4 and a weak inhibitor of CYP2D6. In addition, cobicistat inhibits adenosine triphosphate-dependent transporters, **breast cancer resistance protein**, and P-glycoprotein (Pgp), and the organic anion transporting polypeptides OAT1B1 and OAT1B3. By inhibiting Pgp intestinal secretion, cobicistat increases the bioavailability of tenofovir alafenamide (TAF) by 2.2-fold, so the 10-mg dose of TAF in Genvoya is equivalent to the 25-mg dose of TAF found in other coformulated, TAF-containing preparations that do not contain cobicistat.<sup>1,2</sup> The potential exists for multiple drug interactions when using cobicistat. Before cobicistat is administered, a patient's medication profile should be carefully reviewed for potential interactions and overlapping toxicities with other drugs.
- While cobicistat and ritonavir are both strong inhibitors of CYP3A4,<sup>3</sup> they are not interchangeable,<sup>4,5</sup> and administration with either atazanavir or darunavir may result in different drug interactions. Darunavir induces cobicistat clearance and leads to a shorter cobicistat half-life; atazanavir decreases cobicistat clearance and increases cobicistat half-life.<sup>6</sup>**

- Cobicistat is a stronger Pgp inhibitor than ritonavir and therefore has a greater effect than ritonavir on intestinal absorption of drugs that are metabolized by Pgp, like dabigatran.<sup>7</sup> Cobicistat boosts dolutegravir concentrations to a greater extent than ritonavir, presumably also due to a Pgp interaction.<sup>8</sup>
- Dexamethasone induces CYP3A4 and decreases cobicistat half-life, potentially decreasing concentrations of the antiretroviral (ARV) drugs that cobicistat is boosting. Cobicistat inhibits the clearance of corticosteroids whose exposures are significantly increased by CYP3A4 inhibitors (e.g., fluticasone), potentially leading to adrenal suppression or Cushing syndrome.

### Major Toxicities

- *More common:* Nausea, vomiting, diarrhea, abdominal pain, anorexia.
- *Less common (more severe):* New onset or worsening of renal impairment when used with tenofovir disoproxil fumarate. Rhabdomyolysis; increased amylase and lipase.

### Resistance

Not applicable. Cobicistat has no antiviral activity. Its sole use is as a pharmacokinetic enhancer of ARV drugs.

### Pediatric Use

#### Approval

Cobicistat alone (as Tybost), or cobicistat coformulated with atazanavir (as Evotaz) or darunavir (as Prezcofix), or as a component of Stribild, is not Food and Drug Administration (FDA)-approved for use in children aged <18 years. Cobicistat as a component of Genvoya is FDA-approved at the adult dose in children aged  $\geq 6$  years and weighing  $\geq 25$  kg. The safety of cobicistat as a component of Genvoya in this age and weight group suggests the cobicistat component would be safe in other formulations, as well.<sup>9</sup>

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## Ritonavir (RTV, Norvir) (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 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

### Dosing Recommendations

#### Ritonavir as a Pharmacokinetic Enhancer:<sup>a</sup>

- Ritonavir is used as a pharmacokinetic enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See other sections of the [Drug Appendix](#) for information about ritonavir dosing with specific PIs.

#### Formulation Considerations:

- The oral solution contains propylene glycol and ethanol.
- The oral powder is preferred over the oral solution for children who cannot swallow the tablets and who need a dose of at least 100 mg, because the oral powder does not contain propylene glycol or ethanol.
- Ritonavir oral powder should be used only for dosing increments of 100 mg and cannot be used for doses <100 mg.

### Selected Adverse Events

- Gastrointestinal intolerance, nausea, vomiting, diarrhea
- Paresthesia (circumoral and extremities)
- Hyperlipidemia, especially hypertriglyceridemia
- Hepatitis
- Asthenia
- Taste perversion
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Toxic epidermal necrolysis and Stevens-Johnson syndrome

### Special Instructions

- Administer ritonavir with food to increase absorption and reduce gastrointestinal adverse effects.
- Do not administer** ritonavir with cobicistat or drugs that contain cobicistat (e.g., Stribild, Genvoya, Prezcoibix, Evotaz).
- If ritonavir is prescribed with didanosine, administer the drugs 2 hours apart.
- Do not refrigerate** ritonavir oral solution; store at 68° F to 77° F (20° C to 25° C). Shake the solution well before use.
- Ritonavir oral powder should be mixed with a soft food (e.g., apple sauce, vanilla pudding) or a liquid (e.g., water, chocolate milk, infant formula) to help mitigate the bitter taste. Administer or discard within 2 hours of mixing.



#### To Increase Tolerability of Ritonavir Oral Solution in Children:

- Mix solution with milk, chocolate milk, ice cream, or vanilla or chocolate pudding.
- Before administering ritonavir, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds. Another option is to give a child peanut butter to coat the mouth.
- After administration, give strong-tasting foods (e.g., maple syrup, cheese).
- Check food allergy history before making these recommendations.
- Counsel parents or patients that the bad taste will not be completely masked.

#### Metabolism/Elimination

- Cytochrome P (CYP) 3A and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer.

#### Ritonavir Dosing in Patients with Hepatic Impairment:

- Ritonavir is primarily metabolized by the liver. No dose adjustment is necessary in patients with mild or moderate hepatic impairment. Data are unavailable on ritonavir dosing for adult or pediatric patients with severe hepatic impairment. Use caution when administering ritonavir to patients with moderate-to-severe hepatic impairment.

<sup>a</sup> Ritonavir has antiviral activity, but it is not used as an antiviral agent (see text).

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

- **Metabolism:** Ritonavir is extensively metabolized by (and is one of the most potent inhibitors of) hepatic cytochrome P (CYP) 450 3A. There is potential for multiple drug interactions with ritonavir.
- Before ritonavir is administered, a patient's medication profile should be carefully reviewed for potential interactions with ritonavir and overlapping toxicities with other drugs.
- Ritonavir and cobicistat **are not interchangeable** and may result in different drug interactions.<sup>1</sup>
- Avoid concomitant use of intranasal or inhaled fluticasone, because adrenal insufficiency has been reported.<sup>2</sup> Use caution when prescribing ritonavir with other inhaled steroids. Limited data suggest that beclomethasone may be a suitable alternative to fluticasone when a patient who is taking ritonavir requires an inhaled or intranasal corticosteroid.<sup>3,4</sup> **See Drug Interactions between Protease Inhibitors and Other Drugs in the Adult and Adolescent 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, pancreatitis, and hepatitis (life-threatening in rare cases). Allergic reactions, including bronchospasm, urticaria, and angioedema. Toxic epidermal necrolysis and Stevens-Johnson syndrome have occurred.<sup>5</sup>

## Resistance

Resistance to ritonavir is not clinically relevant when the drug is used as a pharmacokinetic (PK) enhancer of other antiretroviral (ARV) medications.

## Pediatric Use

### Approval

Ritonavir has been approved by the Food and Drug Administration for use in the pediatric population.

### Efficacy: Effectiveness in Practice

Use of ritonavir as the sole protease inhibitor (PI) in ARV therapy in children **is not recommended**. Although ritonavir has been well studied in children as an ARV agent, it is no longer used as a sole PI for therapy because ritonavir is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. In addition, poor palatability of the liquid preparation and a large pill burden with the tablets (the adult dose is six tablets, twice daily) limit its use as a sole PI. However, in both children and adults, ritonavir is recommended as a PK enhancer for use with other PIs. Ritonavir is a CYP3A inhibitor and functions as a PK enhancer by slowing the metabolism of the PIs.

### Dosing

Pediatric dosing regimens, including boosted fosamprenavir, tipranavir, darunavir, atazanavir, and the PI co-formulation lopinavir/ritonavir (LPV/r), are available. For more information about individual PIs, see other sections of the [Drug Appendix](#).

### Toxicity

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir 400 mg twice daily.<sup>5</sup> Potentially life-threatening arrhythmias have been reported in premature newborn infants treated with LPV/r; the use of LPV/r **is not recommended** until the gestational age of 42 weeks.<sup>6,7</sup> Co-administration of ritonavir with other drugs that prolong the PR interval (e.g., macrolides, quinolones, methadone) should be undertaken with caution because it is unknown how co-administering any of these drugs with ritonavir will affect the PR interval. In addition, ritonavir should be used with caution in patients who may be at increased risk of developing cardiac conduction abnormalities, such as patients who have underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

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## Appendix B: Acronyms (Last updated May 22, 2018; last reviewed May 22, 2018)

### Drug Name Abbreviations

Abbreviation	Full Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
<b>BIC</b>	<b>bictegravir</b>
COBI or /c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
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

## General Terms

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
BID	twice daily
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
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

<b>Acronym</b>	<b>Term</b>
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® 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**

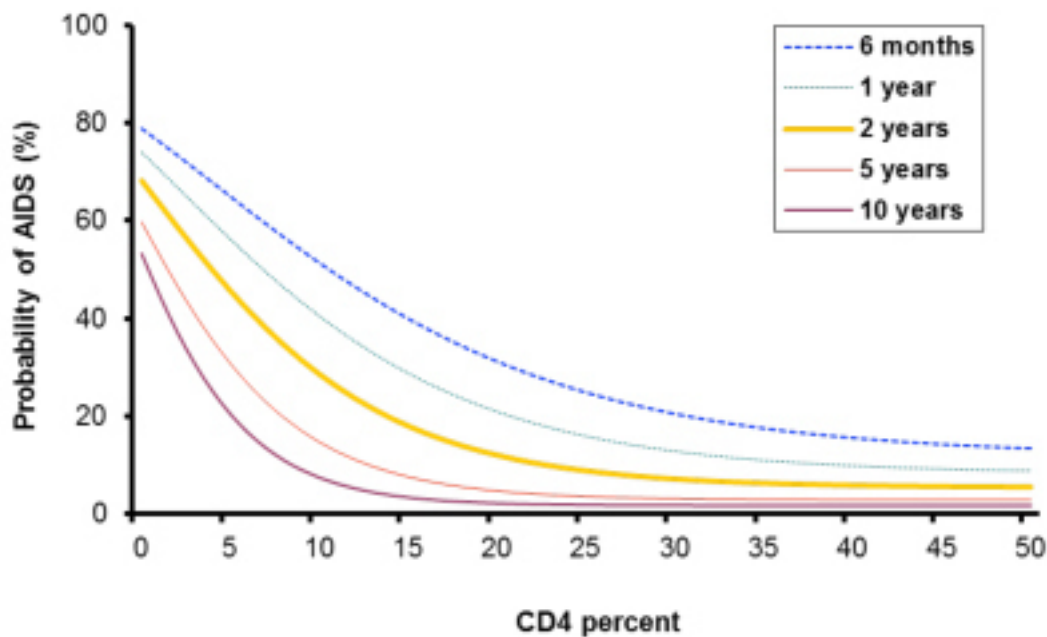


Figure modified from *Lancet* 2003;362:1605-1611

**Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

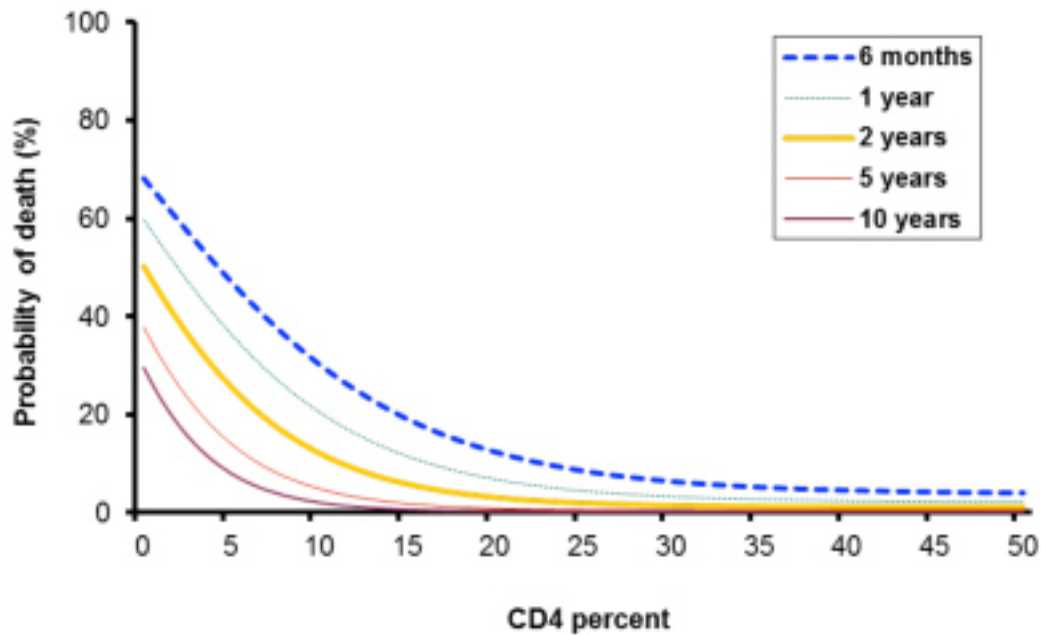


Figure modified from *Lancet* 2003;362:1605-1611

**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\***

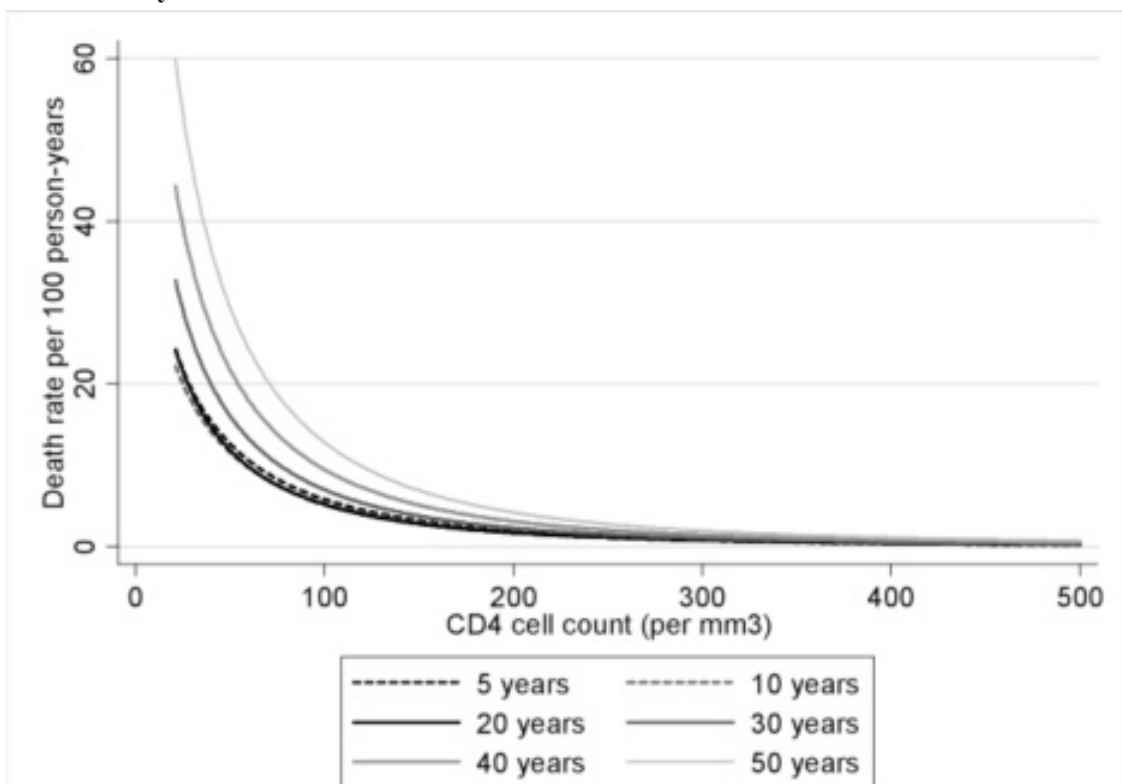


Figure modified from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis.* 2008;197:398-404.

**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**

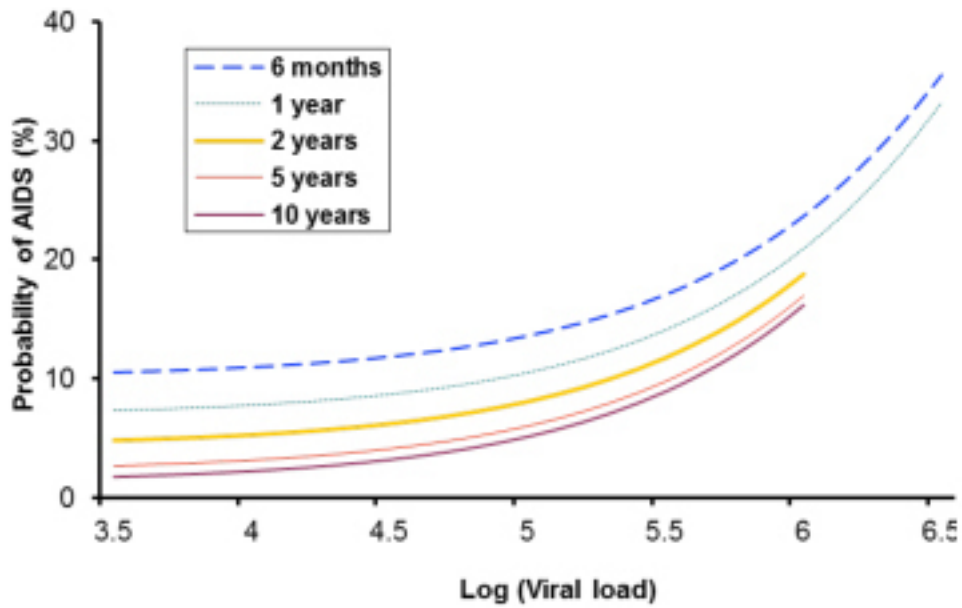


Figure modified from *Lancet* 2003;362:1605-1611

**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**

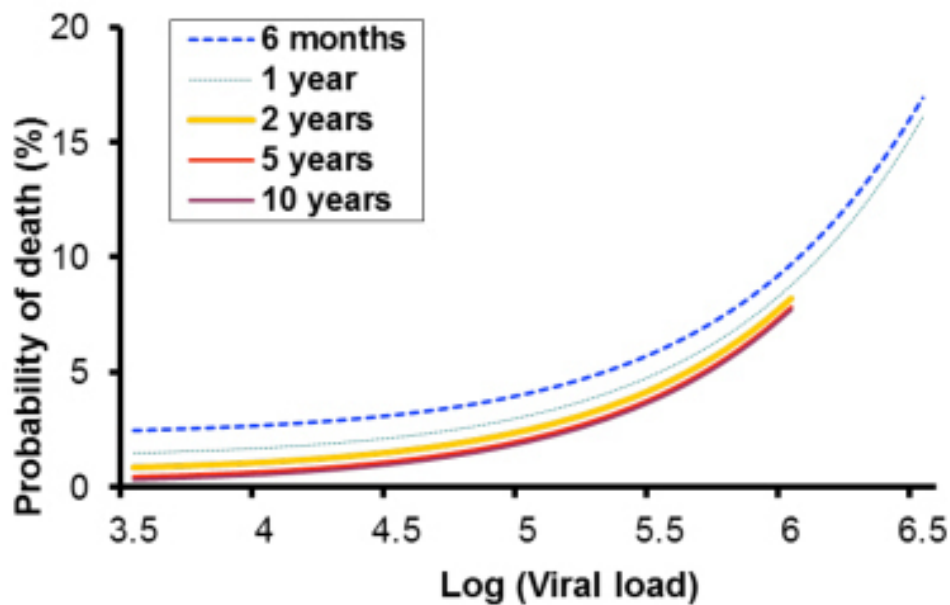


Figure modified from *Lancet* 2003;362:1605-1611