



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

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## What's New in the Pediatric Guidelines (Last updated September 12, 2019; last reviewed September 12, 2019)

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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:

### September 12, 2019

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

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

- Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children, Figure 1, and the associated text now include new recommendations for the use of bictegravir and dolutegravir in children:
  - The fixed-dose combination (FDC) tablet Biktarvy is now a *Preferred* integrase strand transfer inhibitor (INSTI)-based regimen for adolescents aged  $\geq 12$  years and weighing  $\geq 25$  kg (**AI**) and an *Alternative* INSTI-based regimen for children aged  $\geq 6$  years and weighing  $\geq 25$  kg (**AI**).
  - Dolutegravir plus two nucleoside reverse transcriptase inhibitors is now an *Alternative* INSTI-based regimen for children aged  $\geq 3$  years and weighing  $\geq 20$  kg to  $< 25$  kg (**AI\***). It was previously recommended only for children weighing  $\geq 25$  kg. Data are limited on the efficacy and safety of administering dolutegravir to children weighing  $\geq 20$  kg to  $< 25$  kg and dolutegravir pharmacokinetics vary more among children in this weight group than among those weighing  $\geq 25$  kg.
- Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children now includes information about Biktarvy.

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

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

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

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

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

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

### **April 16, 2019**

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

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

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

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

### **Introduction**

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

needs related to immigration.

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

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

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

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

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

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

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

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

## ***Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV***

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

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

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

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

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

## ***Recognizing and Managing Antiretroviral Treatment Failure***

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

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

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

- For children who are receiving twice-daily liquid formulations of abacavir, the Panel no longer recommends a specific time frame for when clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts should switch from twice-daily to once-daily dosing. Previously, the Panel recommended making this switch at 6 months or 24 weeks.
- Efavirenz 600 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (Symfi) is now available, and this FDC tablet is approved by the FDA for use in children and adolescents weighing  $\geq 40$  kg.
- The Panel has added guidance about the use of efavirenz 400 mg/lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg (Symfi Lo) in children and adolescents weighing  $\geq 40$  kg with sexual maturity ratings of 1 to 3. Therapeutic drug monitoring is suggested by some Panel members when Symfi Lo is used in pediatric patients weighing  $\geq 40$  kg.
- Etravirine is now approved by the FDA for use in ARV-experienced children aged  $\geq 2$  years and weighing  $\geq 10$  kg.

- The Panel recommends using an investigational dose of dolutegravir (50 mg) for children and adolescents weighing  $\geq 25$  kg who are ARV-naive or ARV-experienced but INSTI-naive and who are not being treated with uridine diphosphate glucuronyl transferase 1A1 or cytochrome P450 3A inducers. This recommended dose is based on interim data from ongoing trials that indicate that using the FDA-approved dose of dolutegravir 35 mg in patients weighing  $\geq 30$  kg to 40 kg may result in suboptimal trough concentrations. Dolutegravir is not approved by the FDA for use in children weighing  $< 30$  kg.
- Lopinavir/ritonavir (Kaletra) is approved by the FDA for use in neonates who have attained a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, if no alternatives are available for infants who have not met these age thresholds, some members of the Panel recommend using lopinavir/ritonavir oral solution immediately after birth in combination with careful monitoring; see the [lopinavir/ritonavir](#) section for additional information.
- The Panel has provided updated information about the investigational dosing of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) that is currently being studied in children aged 6 years to  $< 12$  years and weighing  $\geq 25$  kg, and children and adolescents aged 12 years to  $< 18$  years and weighing  $\geq 35$  kg; however, Biktarvy is not approved by the FDA for pediatric use.
- New sections were added for doravirine and ibalizumab; however, these drugs are not yet approved for use in children or adolescents aged  $< 18$  years.
- Older ARV drugs that the Panel **does not recommend** for use in children because of unacceptable toxicities, inferior virologic efficacy, pill burden, pharmacologic concerns, and/or limited pediatric data have been moved into an Appendix section titled Archived Drugs; data on these drugs will no longer be reviewed by the Panel. The drugs moved into this section include didanosine, enfuvirtide, fosamprenavir, indinavir, nelfinavir, saquinavir, stavudine, and tipranavir.

## December 14, 2018

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

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

- A new bulleted recommendation was added to emphasize that partners of pregnant women should be encouraged to undergo HIV testing if their HIV status is unknown.
- Risk of HIV exposure should be assessed in all women who are considering becoming pregnant, as well as in all pregnant women who previously tested HIV negative. Women with risk factors for HIV acquisition should receive prevention counseling and appropriate interventions, including pre-exposure prophylaxis, if indicated.
- The indications for third-trimester HIV retesting have been updated to include women who are incarcerated or who reside in states that require third-trimester testing. Data about gaps in perinatal HIV testing suggest that providers should be proactive in assessing a woman's HIV acquisition risk and implementing third-trimester HIV retesting in areas where it is not routine, when indicated.

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

- The use of an assay that detects HIV non-B subtype viruses or Group O is now recommended for known or suspected maternal non-B subtype virus or Group O infections (RNA nucleic acid tests (NATs) and dual-target total DNA/RNA tests).
- The case definition for indeterminate HIV infection in children aged  $< 18$  months has been added.

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

- Zidovudine plus lamivudine plus raltegravir is now a recommended empiric HIV therapy option for neonates who are at a higher risk of perinatal HIV transmission. Information has been added to this section about the use and safety of raltegravir in infants.
- Some Panel members opt to discontinue nevirapine, raltegravir, and/or lamivudine when the birth HIV NAT returns negative, while others choose to continue empiric HIV therapy for 6 weeks. In all cases where the newborn is at a higher risk of HIV acquisition, zidovudine should be continued for 6 weeks. The Panel recommends consulting with an expert in pediatric HIV when making a decision about the duration of empiric HIV therapy.
- Table 11. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn and Table 12. Newborn Antiretroviral Dosing Recommendations have been revised according to updated recommendations for the treatment of newborns with HIV infection and newborns who are at low risk or high risk of perinatal HIV transmission.

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

- Two new tables in Appendix A provide information about FDC formulations of ARV drugs and their use in children.
- [Appendix A, Table 1](#). Antiretrovirals Available in Fixed-Dose Combination Tablets organizes information as grid, with ARV drugs listed alphabetically by class across the top and available FDCs listed on the left.
- [Appendix A, Table 2](#). Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents columns include dosages of FDC component drugs, the minimum body weight requirements for these drugs, pill size (when available), and food requirements.