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

Developed by the HHS Panel on Antiretroviral Therapy and
Medical Management of @efiaobk Ifsfkd tfqe EFS—A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

**How to Cite the Pediatric Guidelines:**

Panel on Antiretroviral Therapy and Medical Management of @efiaobk Ifsfkd tfqe EFS. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed (insert date) [include page numbers, table number, etc. if applicable]

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

## What's New in the Pediatric Guidelines (Last updated April 27, 2017; last reviewed April 27, 2017)

Revisions to the March 1, 2016, *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* include key updates to several sections. Text and references throughout the document were updated to include relevant new data and publications. In response to community input, edits were made to continue to incorporate People First Language, which focuses on the person rather than the disease and recognizes the importance of language in empowering individuals and reducing stigma. Examples of language edits include changes from use of "HIV-infected children" to "children living with HIV", "children with HIV", or "children with HIV infection." Consequently, there was also a change in the Panel's name to the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Key section updates are summarized below:

### Diagnosis of HIV Infection

- The section has been updated to clarify recommendations for diagnostic testing of infants at higher risk of perinatal HIV transmission and those who have received multidrug antiretroviral prophylaxis. The infant testing algorithm is illustrated in a new figure, Figure 1. Recommended virologic testing schedules for infants exposed to HIV by perinatal HIV transmission risk.

### What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children

- The section has been updated to include the use of age and weight limitations in the Panel's recommendations. Although age can be used as a rough guide, body weight is the preferred determinant of the recommendation for selecting a specific drug, when available, except for infants less than 14 days of age.
- Drug-specific sections about efficacy in clinical trials, adverse events and other factors and considerations were moved to Appendix A: Pediatric Antiretroviral Drug Information.
- The Panel has updated Preferred regimens based on recent Food and Drug Administration (FDA) approvals, efficacy, ease of administration and acceptable toxicity, see Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children and Figure 2. Preferred and Alternative Regimens by Age and Drug Class. Significant updates include the following:
    - The Panel has added a recommended initial regimen of nevirapine plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) for infants aged birth to <14 days, but notes that there are currently no clinical trial data suggesting that initiating treatment within the first 14 days of life improves outcome compared to starting after 14 days of age. The Panel recommends that a change from nevirapine to lopinavir/ritonavir should be considered after 14 days of life and 42 weeks post-gestational age based on infant genotype and the better outcomes of lopinavir/ritonavir in children aged <3 years.
    - Dolutegravir plus 2 NRTIs has been added as a Preferred initial regimen for children aged ≥6 to <12 years (weighing ≥30 kg).
    - Tenofovir alafenamide has been added as a Preferred NRTI for adolescents aged >12 years.
    - Efavirenz or lopinavir plus 2 NRTIs are now classified as Alternative rather than Preferred regimens for children ≥3 years to <12 years of age. Twice daily boosted darunavir or raltegravir plus 2 NRTIs were changed from Preferred to Alternative regimens for children ≥6 years to <12 years of age.

- o Didanosine plus (lamivudine or emtricitabine) has been added to 2-NRTI regimens for use in Special Circumstances in Combination with Additional Drugs.

## Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV

- The section now presents information about adherence monitoring in Table 11. Evidence-based Approaches for Monitoring Medication Adherence.

## Management of Children Receiving Antiretroviral Therapy

- The section on Modifying Antiretroviral Regimens in Children with Sustained Virologic Suppression on Antiretroviral Therapy has been updated to include examples of new options for regimen modification.
- The section on Recognizing and Managing Antiretroviral Treatment Failure has been streamlined and updated with information about new regimen options, see Table 16. 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.

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

- Use of patient pharmacogenetic profile for the selection of the dose of certain ARV drugs (e.g., efavirenz) was added to the scenarios where targeted therapeutic drug monitoring can be considered.
- Table 17. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations was updated to include additional drugs and the format has been changed to present data as shown in the original source.

## Pediatric Antiretroviral Drug Information

Drug sections in Appendix A: Pediatric Antiretroviral Drug Information were reviewed and updated to include new pediatric data, dosing, and safety information as well as some drug-specific information that was previously located in What Drugs to Start: Initial Combination Therapy for Antiretroviral Treatment-Naive Children. Interim updates were made in April 2016 and September 2016 to include information about newly released drugs (Odefsey and Descovy) and updated formulations (low-strength Truvada) and new tablet strengths of dolutegravir (10 and 25 mg). Other significant changes are summarized below:

- Zidovudine now includes a table with simplified weight band dosing (for use aged birth to 4 weeks) for infants who are ≥35 weeks gestational age.
- Maraviroc has been updated to include new dosage forms and pediatric dosing information following FDA approval for use in children aged ≥2 years and weighing ≥10 kg.
- Raltegravir now includes the investigational dose for neonates ≥37 weeks of gestation and weighing ≥2 kg under study in IMPAACT P1110.

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# Members of Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (Last updated April 27, 2017; last reviewed April 27, 2017)

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 |
| Allison L. Agwu, MD, SCM | Johns Hopkins School of Medicine, Baltimore, MD |
| Ben Banks, MPH, BSW | Ashland, VA |
| Edmund V. Capparelli, PharmD | 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 |
| 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 |
| Natella Rakhmanina, MD, PhD | Children's National Medical Center, Washington, DC |
| Richard M. Rutstein, MD | Children's Hospital of Philadelphia, Philadelphia, PA |
| Dorothy Shaw, BA | 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 |

# Members of Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (Last updated April 27, 2017; last reviewed April 27, 2017)

| Members from the Department of Health and Human Services | |
|---|---|
| Yodit Belew, MD | Food and Drug Administration, Silver Spring, MD |
| Devasena Gnanashanmugam, MD | National Institutes of Health, Bethesda, MD |
| Mindy Golatt, MPH, MA, RN, CPNP | Health Resources and Services Administration, Rockville, MD |
| Patrick Jean-Philippe, MD | National Institutes of Health, Bethesda, MD |
| Charley LeBaron, MD | Centers for Disease Control and Prevention, Atlanta, GA |
| Linda Lewis, MD | Food and Drug Administration, Silver Spring, MD |
| George K. Siberry, MD, MPH | National Institutes of Health, Bethesda, MD |

| Non-Voting Observer | |
|---|---|
| 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 HIV-Infected Children Financial Disclosure (Last updated April 27, 2017; last reviewed April 27, 2017)

| Name | Panel Status | Company | Relationship |
|---|---|---|---|
| **Abrams, Elaine J.** | M | ViiV Advisory Board | Advisory Board Member |
| **Agwu, Allison L.** | M | None | N/A |
| **Banks, Ben** | M | None | N/A |
| **Belew, Yodit** | M | None | N/A |
| **Brophy, Jason** | NVO | Abbott Labs | Research Support |
| **Capparelli, Edmund V.** | M | 1. Alexion<br>2. Cempra<br>3. The Medicines Company<br>4. Gilead | 1. Consultant<br>2. DSMB Member<br>3. DSMB Member<br>4. Consultant |
| **Chadwick, Ellen G.** | M | Abbott Labs | Stockholder and stock options |
| **Chakraborty, Rana** | M | Gilead | Research Support |
| **Clarke, Diana F.** | M | Merck | Travel Support |
| **Flynn, Patricia M.** | M | Merck, Sharp & Dohme | Consultant |
| **Foca, Marc D.** | M | None | N/A |
| **Gnanashanmugam, Devasena** | 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 | None | N/A |
| **LeBaron, Charley** | M | None | N/A |
| **Lewis, Linda** | HHS | None | N/A |
| **McAuley, James B.** | M | None | N/A |
| **Melvin, Ann J.** | VC | Gilead | Research Support |
| **Mirochnick, Mark** | M | 1. Merck<br>2. ViiV | 1. DSMB Member<br>2. DSMB Member |
| **Mofenson, Lynne M.** | M | None | N/A |
| **Palumbo, Paul** | M | 1. Gilead<br>2. ApoPharma | 1. DSMB Member<br>2. DSMB Member |
| **Paul, Mary E.** | VC | None | N/A |
| **Peters, Vicki B.** | M | None | N/A |
| **Rakhmanina, Natella** | M | 1. Pfizer<br>2. Gilead | 1. Research Support<br>2. Research Support |
| **Ruel, Theodore D.** | VC | None | N/A |
| **Rutstein, Richard M.** | M | None | N/A |
| **Shaw, Dorothy** | M | None | N/A |
| **Siberry, George K.** | HHS | None | N/A |

## HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children Financial Disclosure (Last updated April 27, 2017; last reviewed April 27, 2017)

| Name | Panel Status | Company | Relationship |
|---|---|---|---|
| **Storm, Deborah** | NVO | 1. Eli Lilly and Company<br>2. Merck<br>3. Roche | 1. Stockholder<br>2. Stockholder<br>3. Stockholder and stock options |
| **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 April 27, 2017; last reviewed April 27, 2017)

These updated Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection address the use of antiretroviral therapy (ART) for infants, children, and adolescents living with HIV. In general, these guidelines are appropriate for the care and management of youth with sexual maturity rating (SMR, formerly Tanner staging) I to III, whereas the guidelines developed by the Panel for the Use of Antiretroviral Agents in HIV-1 Infected 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 AIDS*info* website at http://aidsinfo.nih.gov.

The AIDS*info* 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,[1] (2) the use of ARV agents in adolescents and adults with HIV,[2] (3) the use of ARV drugs in pregnant women with HIV,[3] and (4) the prevention and treatment of OIs in adolescents and adults with HIV.[4] These guidelines are developed for the United States and may not be applicable in other countries. The World Health Organization provides guidelines for resource-limited settings at http://www.who.int/hiv/pub/arv/en.

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 morbidity and mortality in children living with HIV in the United States. Mortality in children with perinatal HIV infection has decreased by more than 80% to 90% since the introduction of protease inhibitor-containing combinations and opportunistic and other related infections in children have significantly declined in the era of ART.[5,6] 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 capable of maximally suppressing viral replication in order to prevent disease progression, preserve or restore immunologic function, and prevent the development of drug resistance. At the same time, 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. The use of ARV drugs in pregnant women living with HIV has resulted in a dramatic decrease (to less than 2%) in the rate of HIV transmission to infants in the United States. In addition, children living with HIV are less likely to develop AIDS because of routine and early institution of effective ART.[7,8] Finally, as a group, children living with HIV infection are growing older, bringing 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.[9-11]

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*, intrapartum, and/or postpartum neonatal exposure to ARV drugs in most children with perinatal HIV infection;
- Requirement for use of HIV virologic tests to diagnose perinatal HIV infection in infants younger than 18 months;
- 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 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;
- Differences in the clinical manifestations and treatment of HIV infection secondary to onset of infection 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 infection is complex and evolving rapidly as results of new research are reported, new ARV drugs are approved, and new approaches to treatment are recommended. Clinical trials to define appropriate drug dosing and toxicity in children ranging in age from infancy to adolescence are critical as new drugs become available. As additional ARV drugs become approved and optimal strategies for use of these drugs in children becomes 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 infection 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 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.

## 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** (page 1 of 2)

| Topic | Comment |
|---|---|
| **Goal of the Guidelines** | 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. |
| **Panel Members** | The Panel is composed of approximately 32 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. 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, *ex officio* member of the Panel. The US government representatives are appointed by their respective agencies; nongovernmental members are selected after an open announcement to call for nominations. Each member serves on the Panel for a 3-year term with an option for reappointment. A list of current members can be found in the Panel Roster. |
| **Financial Disclosure** | All members of the Panel submit a financial disclosure statement in writing annually, 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 AIDS*info* website (http://aidsinfo.nih.gov). |
| **Users of the Guidelines** | Providers of care to infants, children, and adolescents living with HIV in the United States |
| **Developer** | Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV—a working group of OARAC |
| **Funding Source** | Office of AIDS Research, NIH and HRSA |
| **Evidence Collection** | A standardized review of recent relevant literature related to each section of the guidelines is performed by a technical assistance consultant (through funding from HRSA) and provided to individual Panel section working groups. The recommendations are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines. |
| **Recommendation Grading** | Described in Table 2. |

**Table 1. Outline of the Guidelines Development Process** (page 2 of 2)

| Topic | Comment |
|---|---|
| **Method of Synthesizing Data** | Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the Panel. The Panel discusses all proposals during monthly teleconferences. Proposals are modified based on Panel discussion and then distributed with ballots to all Panel members for concurrence and additional comments. If there are substantive comments or votes against approval, the recommended changes and areas of disagreement are brought back to the full Panel (by email or teleconference) for additional review, discussion, and further modification to reach a final version acceptable to all Panel members. The recommendations in these final versions represent endorsement from a consensus of members and are included in the guidelines as official Panel recommendations. |
| **Other Guidelines** | These guidelines focus on infants, children, and adolescents in early puberty (SMR I-III) living with HIV. Guidance for treatment for adolescents in late puberty (SMR IV-V) is provided by the Panel on Antiretroviral Guidelines for Adults and Adolescents.<br><br>Separate guidelines outline the use of ART in pregnant women with HIV infection and interventions for prevention of perinatal transmission, ART for nonpregnant adults and postpubertal adolescents with HIV infection, and ARV prophylaxis for those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available on the AIDS*info* website (http://www.aidsinfo.nih.gov). |
| **Update Plan** | The full Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Smaller working groups of Panel members hold additional teleconferences to review individual drug sections or other specific topics (e.g., What to Start). Updates may be prompted by new drug approvals (or new indications, formulations, or frequency of dosing), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and post accompanying recommendations on the AIDS*info* website until the guidelines can be updated with appropriate changes. All sections of the guidelines will be reviewed, with updates as appropriate, at least once yearly. |
| **Public Comments** | A 2-week public comment period follows release of the updated guidelines on the AIDS*info* 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 contactus@aidsinfo.nih.gov. |

## *Basis for Recommendations*

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

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:

1. 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;
2. Supplemental data exist on PKs of the drug in children indicating that systemic exposure in adults and children are similar; and
3. Studies are provided that support the safety of the drug in pediatric patients.[12-14]

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, evidence related to use of ARV drugs is substantially greater from adult studies (especially randomized clinical trials) than from pediatric studies. Therefore, for pediatric recommendations, the following rationale has been used when the quality of evidence from pediatric studies is limited:

### 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 III clinical trial in adults demonstrates a drug is effective in ARV-naive patients and data from a nonrandomized pediatric trial demonstrate adequate and consistent safety and PK data in the pediatric population.

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

- Quality of Evidence Rating II will be used if there are data from well-designed nonrandomized trials or observational cohorts in children.
- Quality of Evidence Rating II* will be used if there are well-designed nonrandomized trials or observational cohort studies in adults with supporting and consistent information from smaller nonrandomized trials or cohort studies with clinical outcome data in children. A rating of II* may be used for quality of evidence if, for example, a large observational study in adults demonstrates 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 AIDS*info* website (http://aidsinfo.nih.gov/ClinicalTrials/) or by telephone at 1-800-448-0440.

**Table 2. Rating Scheme for Recommendations**

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

[a] Studies that include children or children and adolescents, but not studies limited to post-pubertal adolescents

## References


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# Identification of Perinatal HIV Exposure (Last updated April 27, 2017; last reviewed April 27, 2017)

| Panel's Recommendations |
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| • HIV testing early in pregnancy is recommended as standard of care for all pregnant women in the United States **(AII)**.<br>• Repeat HIV testing in the third trimester, before 36 weeks' gestation, should be considered for all HIV-seronegative pregnant women and is recommended for pregnant women who are at high risk of HIV infection **(AII)**.<br>• 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. If results are positive, intrapartum and infant postnatal antiretroviral (ARV) drug prophylaxis should be initiated immediately, pending results of supplemental HIV testing **(AII)**.<br>• 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. If results in mother or infant are positive, infant ARV drug prophylaxis should be initiated immediately, and the mothers should not breastfeed unless supplemental HIV testing is negative **(AII)**. In infants with initial positive HIV viral tests (RNA, DNA), prophylaxis should be stopped and antiretroviral therapy initiated.<br>• When acute maternal HIV infection is suspected during pregnancy, in the intrapartum period, or while breastfeeding, initial testing should be performed with an antigen/antibody combination immunoassay; if the initial testing was performed with an HIV antibody test or supplemental testing is negative, an additional virologic test (RNA, DNA) may be necessary to diagnose HIV infection **(AII)**.<br>• Results of maternal HIV testing should be documented in the newborn's medical record and communicated to the newborn's primary care provider **(AIII)**.<br>• Infant HIV antibody testing to determine HIV exposure should be considered for infants in foster care and adoptees for whom maternal HIV infection status is unknown **(AIII)**. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***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*<br>*† 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 or as early in pregnancy as possible. This provides the best opportunity to prevent infant HIV infection and to identify and start therapy as soon as possible in infants who become infected. 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.[1-6] All HIV testing should be performed in a manner consistent with state and local laws (http://nccc.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.[7,8] 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 infection enables:

- Women living with HIV to receive appropriate antiretroviral therapy (ART) and prophylaxis against opportunistic infections for their own health, which may also decrease risk of transmission to their partners.[2,9,10]

- 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;[4]
- Counseling of women living with HIV about the indications for (and potential benefits of) scheduled elective cesarean delivery to reduce perinatal transmission of HIV;[4,11-13]
- Counseling of women living with HIV about the risks of HIV transmission through breast milk (breastfeeding is not recommended for women with HIV infection living in the United States and other countries where safe alternatives to breast milk are available);[14]
- Initiation of prophylaxis against *Pneumocystis jirovecii* pneumonia beginning at age 4 to 6 weeks in all infants with HIV infection and in those infants exposed to HIV whose HIV infection status remains indeterminate;[15] and
- Early diagnostic evaluation of infants exposed to HIV, as well as testing of partners and other children, to permit prompt initiation of ART in individuals with HIV infection.[1,16,17]

Technological improvements have resulted in increased sensitivity to early infection 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.[18] The guidelines recommend that HIV testing begin with a fourth-generation immunoassay capable of detecting HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen (called an antigen/antibody combination 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 assay and a nonreactive differentiation test should be tested with a Food and Drug Administration-approved HIV nucleic acid test to establish diagnosis of acute HIV infection (http://www.cdc.gov/hiv/pdf/hivtestingalgorithmrecommendation-final.pdf#page=11).

The fourth-generation immunoassay testing for both antigen and antibody 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 (<1 hour) 24 hours a day. If positive, testing for confirmation of infection should be done as soon as possible (as with all initial positive assays). Because older tests have lower sensitivity in the context of recent infection, 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 should be considered for all HIV-seronegative pregnant women. A second HIV test during the third trimester, before 36 weeks' gestation, is recommended[4,19] 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 infection 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 infection, 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 infection.[2,3,20,21]

Women who decline testing earlier in pregnancy should be offered testing again during the third trimester, using a fourth-generation antigen/antibody combination immunoassay, as these tests have a higher sensitivity in the setting of acute infection, compared to older antibody tests.[18,22] When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with the fourth-generation test to diagnose acute HIV infection.

## 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 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).[1-3,5,16]

Every hospital offering intrapartum care and every delivery unit must have access to an HIV test that can be performed rapidly (that is, in an expedited fashion with results available within 1 hour) and is available 24 hours a day. 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 infection and their infants.

The test of choice is the fourth-generation antigen/antibody combination immunoassay. Because it can be done quickly it is sometimes referred to as "expedited," but it requires trained lab staff and may not yet be available in hospitals 24 hours a day. If the fourth-generation antigen/antibody combination immunoassay is not available, initial testing should be performed by the most sensitive expedited or rapid test available.

A positive expedited HIV test result must be followed by a supplemental test.[18] However, immediate initiation of ARV drug prophylaxis for prevention of perinatal transmission of HIV is recommended pending the supplemental result after an initial positive expedited HIV test.[1-6,16] No further testing is required for specimens that are nonreactive (negative) on the initial immunoassay.[18]

## 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 or their newborns should undergo expedited HIV testing with maternal consent (unless state law allows testing without consent).[1,3,4,16] Testing should be done using the fourth-generation antigen/antibody combination immunoassay to screen for established infection and for acute HIV-1 infection; results should be obtained in less than 1 hour. If acute HIV-1 infection is a possibility, then a plasma HIV RNA 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 to 12 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 infection.[4] If supplemental tests are negative and acute HIV infection 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 who are in foster care) or their accuracy cannot be evaluated (e.g., for infants adopted from a country where results are not reported in English), HIV antibody testing is indicated to identify HIV exposure in those infants.[1] If antibody testing is positive, further testing is needed to diagnose HIV infection, or in the case of infants older than 18 months, to confirm HIV infection (see Diagnosis of HIV Infection in Infants).

## *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 infection during pregnancy or lactation.[19,23-26] The fourth-generation antigen/antibody combination immunoassay will detect acute infection more readily than other immunoassays. If acute HIV infection is suspected, and the supplemental test is negative, a plasma HIV RNA test should be sent as well. Women with possible acute HIV infection who are breastfeeding should cease breastfeeding immediately until HIV infection is confirmed or excluded.[14] 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 infection, and their infants, should follow the recommendations in the Perinatal Guidelines.[4]

### 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 infection, 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 April 27, 2017; last reviewed April 27, 2017)

| Panel's Recommendations |
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| • Virologic assays (i.e., HIV RNA and HIV DNA nucleic acid tests) that directly detect HIV must be used to diagnose HIV infection in children younger than 18 months with perinatal HIV exposure; HIV antibody tests should not be used **(AII)**.<br>• Virologic diagnostic testing is recommended for all infants with perinatal HIV exposure at the following ages:<br>  • 14 to 21 days **(AII)**<br>  • 1 to 2 months **(AII)**<br>  • 4 to 6 months **(AII)**<br>• Additional virologic diagnostic testing should be considered for infants at higher risk of perinatal HIV transmission at birth **(AIII)** and 2 to 4 weeks after cessation of antiretroviral prophylaxis **(BIII)**.<br>• A positive virologic test should be confirmed as soon as possible by a repeat virologic test on a second specimen **(AII)**.<br>• Definitive exclusion of HIV infection in non-breastfed infants is based on 2 or more negative virologic tests, with 1 obtained at age ≥1 month and 1 at age ≥4 months, or 2 negative HIV antibody tests from separate specimens obtained at age ≥6 months **(AII)**.<br>• Many experts confirm the absence of HIV infection at 12 to 18 months of age in children with prior negative virologic tests by performing an antibody test to document loss of maternal HIV antibodies **(BIII)**.<br>• Children aged 18 to 24 months with perinatal HIV exposure may 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 (see Diagnostic Testing in Children with Perinatal HIV Exposure in Special Situations) **(AII)**.<br>• 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*<br>***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*<br>*† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents* |

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

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 months. HIV antibody tests, including newer 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.[1,2] 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.[3]

Antigen/antibody combination immunoassays (4th- and 5th-generation tests) which detect HIV-1/2 antibodies as well as HIV-1 p24 antigen are not recommended for infant diagnosis in the United States; the sensitivity of the antigen component in the first months of life is less than that of HIV NAT tests and antibody tests cannot be used for infant diagnosis.[4-6]

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 the HIV diagnostic testing described here[7] (see Infant Antiretroviral Prophylaxis in the Perinatal Guidelines).

## *HIV RNA Assays*

HIV quantitative RNA assays detect extracellular viral RNA in the 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.[8] HIV RNA levels <5,000 copies/mL may not be reproducible and should be repeated before they are interpreted as documenting HIV infection in an infant.[9,10] 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).[3,7,8,11]

While HIV DNA PCR remains positive in most individuals receiving antiretroviral (ARV) treatment, HIV RNA assays could potentially be affected by maternal antenatal treatment or infant combination ARV prophylaxis.[12] In one study, the sensitivity of HIV RNA assays was 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.[8] 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 the 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. HIV RNA assays may be more sensitive than HIV DNA PCR for detecting HIV non-subtype B (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 Food and Drug Administration (FDA)-approved.[13-17]

## *HIV DNA Polymerase Chain Reaction and Related Assays*

HIV DNA PCR is a sensitive technique used to detect specific 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 increases to more than 90% by 2 to 4 weeks of age and to 100% at ages 3 months and 6 months.[7,8,11,15]

Two studies provide 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 3 different regimens of neonatal prophylaxis containing 6 weeks of zidovudine either alone or with 2 or 3 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.[18] Another randomized trial comparing short and long maternal and infant zidovudine prophylaxis regimens in Thailand tested infants at 0 to 5 days, 6 weeks, 4 months, and 6 months. Although there was variability in the infant testing dates, this was independent of the treatment duration. Of the 45 infants with confirmed HIV infection who had negative testing in the first 5 days of life, diagnostic testing was positive at an earlier time point (median 10.5 days) when the mother received less than 7.5 weeks of zidovudine prior to delivery and the infant received only 3 days of prophylaxis compared with infants whose mother received longer zidovudine (>7.5 weeks) and/or who received longer infant prophylaxis (at least 4 weeks), where the median time to detection of HIV infection was 24.8 to 42.5 days.[19]

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.[20]

## 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.[21] 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.[22] 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.[23]

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.[24] 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 7 states having greater than 10%.[25] 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.[26] Non-subtype B and Group O strains may also be seen in countries with links to these geographical regions.[27-31] Geographical distribution of HIV groups is available at http://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp.

HIV DNA PCR tests have decreased sensitivity for detection of non-subtype B HIV, and false-negative HIV DNA PCR test results have been reported in infants infected with non-subtype B HIV.[32-34]

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 properly quantify all non-B subtypes and Group O HIV[35-40] (see HIV RNA Monitoring in Children: General Considerations in Clinical and Laboratory Monitoring).

Thus, a real-time PCR assay or qualitative RNA 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 the initial testing is negative using a HIV DNA PCR test and non-subtype B or Group O perinatal exposure is suspected. Two negative HIV antibody tests obtained at age ≥6 months provide further evidence to definitively rule out HIV infection. Clinicians should consult with an expert in pediatric HIV infection; state or local public health departments or the Centers for Disease Control and Prevention (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.[41-43] It also occurs in countries such as France and Portugal, which have large numbers of immigrants from these regions;[44,45] HIV-1 and HIV-2 coinfections may also occur but 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 naturally resistant to several ARV drugs developed to suppress HIV-1.[46-48]

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).[1,49] HIV-2 DNA PCR testing can be arranged by the HIV surveillance program of the state or local health department through their public health laboratory or the CDC because this assay is not commercially available.[50,51] Clinicians should consult with an expert in pediatric HIV infection when caring for infants with suspected or known exposure to HIV-2.[41,52]

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

Confirmation of HIV infection should be based on 2 positive virologic tests from separate blood samples in children younger than 18 months. Children with perinatal HIV exposure aged 18 to 24 months may 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).[1]

HIV infection can be **presumptively** excluded in non-breastfed infants with two or more negative virologic tests (one at age ≥14 days and one at age ≥4 weeks) or one negative virologic test (i.e., negative NAT [RNA or DNA]) at age ≥8 weeks, or one negative HIV antibody test at age ≥6 months.[1,7] *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.[53] Thus, initiation of PCP prophylaxis can be avoided or discontinued if HIV infection is presumptively excluded.

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

For both **presumptive** and **definitive** exclusion of HIV infection, a child must have no other laboratory (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.

For management of infant ARV prophylaxis and prevention of perinatal HIV transmission, see the Infant Antiretroviral Prophylaxis section in the Perinatal Guidelines.[54,55]

Figure 1 summarizes the timing of virologic diagnostic testing described in the following text.

### *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**,[56-61] 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
- Were diagnosed with acute HIV infection during pregnancy
- Who had detectable HIV viral load close to the time of delivery
- Who received combination ARV drugs and did not have sustained viral suppression

As described in the text above on virologic assays, 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 high risk of *in utero* infection, birth testing identified 66.4% of infants with HIV infection.[18] Prompt diagnosis is critical to allow for discontinuing ARV prophylaxis and instituting early antiretroviral therapy (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.[15,56,57]

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

The diagnostic sensitivity of virologic testing increases rapidly by age 2 weeks,[7] and early identification of infection 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 this age is intended to maximize the detection of infants with HIV infection.[8,62] 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,[8] and 68% of infants with HIV infection in the second study.[18] 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.

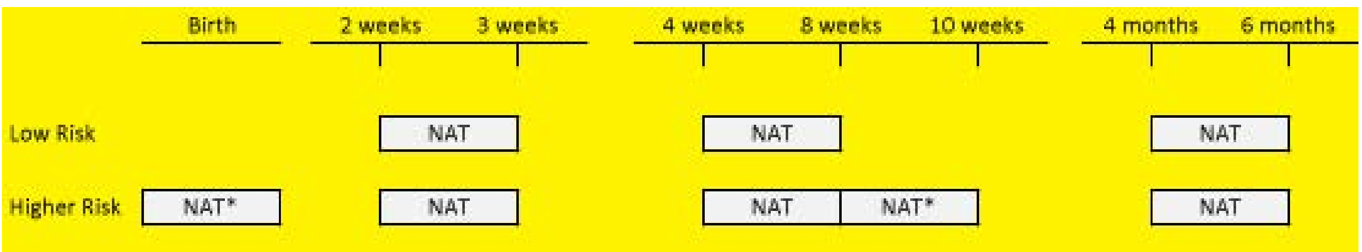
For infants at **higher risk of perinatal HIV transmission**, the Panel suggests an additional virologic test 2 to 4 weeks after cessation of ARV prophylaxis (i.e., at 8–10 weeks of age) given the increased risk of infection and the concern that ARV prophylaxis, particularly combination ARV prophylaxis, may reduce the sensitivity of testing during prophylaxis.[7,8,18] In these situations, many experts recommend 1 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 2 negative virologic tests (1 at age ≥14 days and 1 at age ≥4 weeks) or 1 negative test at age ≥8 weeks can be viewed as **presumptively** uninfected and will not need PCP prophylaxis, 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.

**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, were diagnosed with acute HIV infection during pregnancy, who had detectable HIV viral loads close to the time of delivery, or 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

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

Two or more negative HIV antibody tests performed in non-breastfed infants at age ≥6 months can also be used to **definitively** exclude HIV infection in children with no clinical or virologic laboratory-documented evidence of HIV infection.[63,64]

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

Some experts confirm the absence of HIV infection in infants 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.[1] In a recent study, the median age at seroreversion was 13.9 months.[65] 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.[65-68]

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

### *Late Seroreversion (≤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).[65-68] In one study, 14% of children with HIV exposure who were uninfected seroreverted after age 18 months.[65] 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) will be necessary to definitively exclude or confirm HIV infection in children with perinatal HIV exposure at age 18 to 24 months in situations such as lack of prior testing history or clinical suspicion of HIV infection.

### *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 children who are uninfected from 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.[32-34] The diagnostic approach in these situations is discussed above 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 do so (e.g., women from communities in which breastfeeding is the norm, women who fear that not breastfeeding would be a stigma, or women who fear that not breastfeeding would raise suspicion about the possibility of 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).[69-72] Breast milk from a donor with unrecognized HIV infection at the time of donation is an additional potential risk factor. Infants who are breastfed by women living with HIV should undergo immediate HIV diagnostic testing, and counseling to cease 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), the potential transfer of maternal antibody from breast milk as well as the possibility of performing the testing during acute HIV infection; thus, a NAT would be the choice for the initial test. The receipt of postnatal ARV prophylaxis may delay the detection of HIV infection (see Infant

Antiretroviral Prophylaxis in the Perinatal Guidelines).[73-75]

### Premastication

Receipt of solid food premasticated or prechewed by a caregiver living with HIV has been documented to be associated with risk of HIV transmission.[76-81] 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 (which could occur in countries in which the administration of contaminated blood products is a possibility). 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 needlesticks, 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.[82]

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.[1,83] 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).[84]
- 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 (HIV qualitative RNA assay) 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 CDC/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.[1,85] 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).[50,51]

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# Clinical and Laboratory Monitoring of Pediatric HIV Infection

**(Last updated April 27, 2017; last reviewed April 27, 2017)**

**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 infection 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-naive patients **(AII)**. Genotypic resistance testing is preferred for this purpose **(AIII)**.
- After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical adverse effects and 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 value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years **(AII)**.
- 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 coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered **(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† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

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

Laboratory monitoring of children living with HIV poses unique and challenging issues. In particular, 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, and general laboratory monitoring as well as clinical monitoring of children with HIV infection, relevant to both those who are newly diagnosed and those who are receiving antiretroviral therapy (ART).

## Clinical and Laboratory Monitoring of Children Living With HIV

**Absolute CD4 cell count and plasma HIV RNA (viral load) should be measured at the time of diagnosis of HIV infection and, if a child is <u>not</u> started on ART after diagnosis, <u>this monitoring should be repeated</u> 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-naive patients (AII). Genotypic resistance testing is preferred for this purpose (AIII).**

### Initial Evaluation of Newly Diagnosed Children

Children recently diagnosed with HIV should be evaluated with measurement of CD4 cell count and plasma viral load; evaluation of growth and development for signs of HIV-associated change; and laboratory evaluation of HIV-associated conditions including anemia, leukopenia, thrombocytopenia, hypoalbuminemia, elevated glucose, transaminases, or creatinine, and HIV-associated nephropathy (urinalysis). In addition, children with HIV infection 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 ARV drug history including exposure to medications for prevention of mother-to-child 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).[1]

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

In the event that 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 benefit. 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 gap might help identify nucleoside reverse transcriptase inhibitor-associated lactic acidosis. With use of tenofovir disoproxil fumarate, creatinine may increase, phosphate 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 particular ARV drug, see Tables 13a-13l in Management of Medication Toxicity or Intolerance.

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

**After initiation of ART, or after a change in ART regimen, children should be evaluated for clinical AEs 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 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 dialogue between providers and 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*

While data are limited on which to base an exact recommendation about precise timing, 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. The selection of laboratory chemistry tests is regimen-specific (see above). Evaluation of hepatic transaminases is recommended at 2 weeks and 4 weeks for patients starting treatment that includes nevirapine (see Nevirapine in Appendix A: Pediatric Antiretroviral Drug Information). Plasma viral load monitoring is important as a marker of response to ART because a fall 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.

**Children on ART should be monitored for therapy adherence, effectiveness (by CD4 cell count and plasma viral load), and toxicities (by history, physical, and selected laboratory tests) routinely every 3 to 4 months for the first 2 years (AII*).**

CD4 count improvement is influenced by the baseline value at the time of initiation of ART; children with very low CD4 counts may take more than one year to achieve their highest values after viral load suppression.[2]

**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).**

### *Laboratory Monitoring of Patients Receiving 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 cell count can be monitored less frequently (every 6–12 months) in children and youth who are adherent to therapy and have CD4 cell value well above the threshold for OI risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years.

### *Laboratory Monitoring of Patients Who Are Stable on Long-Term Antiretroviral Therapy*

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 a year.[3-9]

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

- Consistent virus suppression for more than 2 years
- CD4 count consistently >300 cells/$mm^3$

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 youth who are adherent to therapy and have CD4 cell value well above the threshold for OI risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years. 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*

**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 antiretroviral agents and available resistance test results must be reviewed when making decisions regarding the choice of new agents (AII).**

**Viral coreceptor (tropism) assays should be used whenever the use of a CCR5 antagonist is being considered (AI*). Tropism assays should also be considered for patients who demonstrate virologic failure while receiving therapy that contains a CCR5 antagonist (AI*).**

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, with follow up including 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 to optimize 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 non-suppression 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.[10]

## Immunologic Monitoring in Children: General Considerations

**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).**

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 infection are considerably higher than values observed in adults without HIV infection (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.[11] 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.[12]

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-naive child with HIV infection (see When to Initiate). A website using the meta-analysis from the HPPM Collaborative Study is available 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 (http://hppmcs.org).[13]

Measurement of CD4 cell count and percentage can be associated with considerable intrapatient variation.[14] Mild intercurrent illness, the receipt of vaccinations, or exercise can produce a transient decrease in CD4 cell count and percentage; thus, CD4 cell count/percentage are best measured when patients are clinically stable. No decision about therapy should be made in response to a change in CD4 cell count/percentage until the change has been substantiated by at least a second 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. During the period of primary infection in adults and adolescents, in the absence of therapy, plasma viral load initially rises to high peak levels and then declines by as much as 2 to 3 $\log_{10}$ copies to reach a stable lower level (the virologic set point) approximately 6 to 12 months after acute infection.[15,16] 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.[17]

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.[18,19] In one prospective study of infants with perinatal infection born prior to ARV drug availability in 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 during the first year of life of 185,000 copies/mL.[20] After the first year of life, plasma viral load slowly declined over the next few years.[20-23] Viral load during the first 12 to 24 months after birth showed an average decline of approximately 0.6 $\log_{10}$ copies/mL per year, followed by an average decline of 0.3 $\log_{10}$ copies/mL per year until age 4 to 5 years. This pattern probably reflects the lower efficiency of an immature but developing immune system in containing viral replication and possibly the rapid expansion of HIV-susceptible cells that occurs with somatic growth.[24]

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.[22] 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.[19] 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.[22,23,25,26]

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

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 twofold (0.3 $\log_{10}$ copies/mL) or more.[27,28] If possible, 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.[29-31]

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, with the exception of the uncommon O subtypes.[32,33] 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 are infected with non-B viral subtypes.[29,34-38] 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 threefold (0.5 $\log_{10}$ copies/mL) in either direction over the course of a day or on different days.[25,28] This biologic variation may be greater in infants and young children with HIV infection. This inherent biologic variability must be considered when interpreting changes in plasma viral load in children. Thus, on repeated testing, only differences greater than fivefold (0.7 $\log_{10}$ copies/mL) in infants younger than 2 years and greater than threefold (0.5 $\log_{10}$ 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.

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 than in children with HIV infection (see the Adult and Adolescent Antiretroviral Guidelines).[39] Temporary viral load elevations ("blips") between the level of detection and 500 copies/mL often are detected in adults[40] 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.

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

| | Entry Into Care[1] | Pre-Therapy[2] | ART Initiation[3] | Weeks 1–2 on Therapy | Weeks 2–4 on Therapy | Every 3–4 Months[4] | Only Required Every 6–12 Months[5] | ARV Switch |
|---|---|---|---|---|---|---|---|---|
| History and Physical | √ | √ | √ | √ | √ | √ | | √ |
| Adherence Evaluation | | √ | √ | √ | √ | √ | | √ |
| CD4 Count | √ | √ | √ | | | √ | | √ |
| Plasma Viral Load | √ | √ | √ | | √ | √ | | √ |
| Resistance Testing | √ | | | | | | | √ |
| CBC with Differential | √ | √ | √ | | √ | √ | | √ |
| Chemistries | √ | √ | √ | | √ | √ | | √ |
| Lipid Panel | √ | | √ | | | | √ | |
| Random Plasma Glucose | | | √ | | | | √ | |
| Urinalysis | √ | | √ | | | | √ | |
| Hepatitis B Screening[6,7] | | √ | | | | | | √ |

[1] See text for details on recommended laboratory tests to obtain.

[2] 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).

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

[4] 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 value well above the threshold for opportunistic infection risk, sustained viral suppression, and stable clinical status for more than 2 to 3 years.

[5] If lipids have been abnormal in the past, more frequent monitoring might be needed. For patients treated with TDF, more frequent urinalysis is considered.

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

[6] When considering starting ARV drugs with activity against hepatitis B, specifically lamivudine-, emtricitabine-, and tenofovir-containing regimens

[7] Recommended only if individual previously demonstrated no immunity to hepatitis B

**Key to Acronyms:** ART = antiretroviral therapy, ARV = antiretroviral, CBC = complete blood count, CD4 = CD4 T lymphocyte

**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–$10^7$ | 25–$10^7$ | 20–$10^7$ | 37–11x$10^7$ |
| **Specimen volume*** | 0.2–1 mL | 0.1–1 mL | 1 mL | 0.5 mL |
| **Manufacturer** | Abbott | bioMerieux | Roche | Siemens |

* **Note:** Smaller volumes for children can be accommodated.

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

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# Treatment Recommendations (Last updated April 27, 2017; last reviewed April 27, 2017)

## General Considerations

Since the introduction of potent combination antiretroviral (ARV) drug regimens in the mid-1990s, the treatment of pediatric HIV infection 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) regimens including at least 3 drugs from at least 2 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.[1-4] In the United States and the United Kingdom, significant declines in morbidity, mortality, and hospitalizations have been reported in children living with HIV between 1994 and 2006, concomitant with increased use of highly active combination regimens.[5-7] As a result, children with perinatal HIV infection are now living into the third and fourth decades of life, and likely 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).[8-11]

ARV drug-resistant virus can develop during ART when viral replication occurs in the presence of subtherapeutic ARV levels associated with 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-naive children who have become infected with a resistant virus.[12-14] Thus, decisions about what drugs to choose in ARV-naive children (see What to Start) and how to best treat ARV-experienced children remain complex. Whenever possible, decisions regarding the management of pediatric HIV infection should be directed by or made in consultation with a specialist in pediatric and adolescent HIV infection. Treatment of ARV-naive children (when and what to start), when to change therapy, and treatment of ARV-experienced children will be discussed in separate sections of the guidelines. For guidance about treatment of adolescents aged ≥13 years, see 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,[15] a randomized clinical trial has provided evidence of benefit with initiation of ART in asymptomatic adults with CD4 cell counts >500 cells/mm$^3$.[16] Similarly, improved outcomes have been shown with initiation of ART in asymptomatic infants between 6 and 12 weeks of age. Although there are fewer available data on the risks and benefits of immediate therapy in asymptomatic children with HIV than in adults, this Panel recommends ART for all children with HIV, with differing strengths of recommendation based on age and CD4 cell counts (see What to Start). Several factors need to be considered in making decisions about the urgency of initiating and changing ART in children, including:

- Severity of HIV disease and risk of disease progression, as determined by age, presence (see When to Initiate) or history of HIV-related illnesses, degree of CD4 immunosuppression, (see Revised Surveillance Case Definition for HIV Infection at http://www.cdc.gov/mmwr/pdf/rr/rr6303.pdf);
- 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, and 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 initiation of therapy;
- 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 decisions related to treatment of children living with HIV, and flexibility should be exercised according to a child's individual circumstances. 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 formulation of 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 I/II 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 cells.[17-19] This was demonstrated when a child with HIV treated with ART at 30 hours of age experienced viremic rebound after more than 2 years of undetectable HIV RNA levels while off ART.[20,21] Some data suggest that the half-life of intracellular HIV proviral DNA is even longer in children with HIV infection than in adults (median 14 months vs. 5–10 months, respectively).[22] Thus, based on currently available data, HIV causes a chronic infection likely requiring treatment for life once a child starts therapy. The goals of ART for children and adolescents 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; and
- Improving quality of life.

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 infection is a regimen containing at least 3 drugs from at least 2 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 may be a preferred regimen for some patients.

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

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 2 classes of drugs (see What to Start), thereby sparing 3 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 levels of ARV medications, which increases the risk of development of drug resistance and 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 and more time can be taken 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 before making changes to the ART regimen.

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# When to Initiate Therapy in Antiretroviral-Naive Children (Last updated April 27, 2017; last reviewed April 27, 2017)

## Overview

The Department of Health and Human Services (HHS) Adult and Adolescent Antiretroviral Guidelines Panel (the Panel) has recommended initiation of therapy for all adults with HIV infection (see the Adult and Adolescent Guidelines). In addition to trials demonstrating benefit of therapy in symptomatic adults and those with lower CD4 T lymphocyte (CD4) cell counts,[1] a randomized clinical trial has provided definitive evidence of benefit with initiation of antiretroviral therapy (ART) in asymptomatic adults with CD4 cell counts >500 cells/mm$^3$. The START trial randomized 4,685 antiretroviral (ARV)-naive adults with HIV (median age 36 years) with CD4 cell counts >500 cells/mm$^3$ to immediately initiate ART or defer ART until the CD4 cell count declined to <350 cells/mm$^3$ 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 vs. 1.8% in the immediate treatment arm. Sixty-eight percent of the primary end points occurred in patients with CD4 cell counts >500 cells/mm$^3$. The risk of Grade 4 events or unscheduled hospital admissions was similar in the two groups.[2] The Panel's recommendation for initiation of therapy for all adults with HIV is also based on the availability of effective ART regimens with improved tolerability, and evidence that effective ART reduces secondary sexual HIV transmission.[3]

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 strength of the recommendation and urgency for immediate initiation varies by age and pretreatment CD4 cell count due to fewer available data in the pediatric population 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 a young age and will likely be life-long. In children under 1 year of age, the benefit of immediate ART has been clearly demonstrated in the CHER trial,[4] but data in older children are more equivocal. The PREDICT trial, which enrolled children aged >1 year (median age 6.4 years), found the risk of clinical progression was extremely low in both children initiating immediate versus delayed (CD4-based) ART and no clinical benefit of immediate ART was observed.[5] However, in an observational study including over 20,000 children aged 1 to 16 years from 19 cohorts in Europe, Southern African and West Africa, immediate ART was associated with lower mortality and better growth in children aged <10 years compared with delaying ART until CD4 count decreased to <350 cells/mm$^3$.[6]

Considerations for aggressive therapy in the early stages of HIV infection in both children and adults include the potential to 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.[7] Early therapy also preserves immune function, preventing clinical disease progression.[8,9] 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.[8,10-12] Conversely, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, 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 Recommendations | | |
|---|---|---|
| **Age** | **Criteria** | **Recommendation** |
| **<12 Months**[a] | Regardless of clinical symptoms, immune status, or viral load | Urgent[b] treatment (**AII** except **AI** for ≥6 weeks to <12 weeks of age) |
| **1 to <6 Years** | CDC Stage 3-defining opportunistic illnesses[c] | Urgent[b] treatment **(AI*)** |
| | CDC Stage 3 immunodeficiency:[d] CD4 <500 cells/mm$^3$ | |
| | Moderate HIV-related symptoms[c] | Treat[e] **(AII)** |
| | CD4 cell count[c] 500–999 cells/mm$^3$ | |
| | Asymptomatic or mild symptoms[c] **and** CD4 cell count[c] ≥1000 cells/mm$^3$ | Treat[e] **(BI*)** |
| **≥6 Years**[e] | CDC Stage 3-defining opportunistic illnesses[c] | Urgent[a] treatment **(AI*)** |
| | CDC Stage 3 immunodeficiency:[d] CD4 <200 cells/mm$^3$ | |
| | Moderate HIV-related symptoms[c] | Treat[b] **(AII)** |
| | CD4 cell count[d] 200–499 cells/mm$^3$ | |
| | Asymptomatic or mild symptoms[c] **and** CD4 cell count ≥500 cells/mm$^3$ | Treat[f] **(BI*)** |

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

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

*† Studies that include children or children and adolescents but not studies limited to post-pubertal adolescents*

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

[a] Treatment of infants ≤2 weeks is a more complex issue and an area of active investigation. See Specific Issues in Antiretroviral Therapy for Neonates

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

[c] See Table 6 for definitions

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

[e] 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.

[f] For initiation of ART for adolescents aged ≥13 years and sexually maturity ratings or 4 or 5, see the Adult and Adolescent Guidelines.

**Key to Acronyms:** CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention

## 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 perinatally infected infants with normal CD4 percentages (>25%) resulted in a 75% reduction in early mortality, compared with delaying treatment until the infants met clinical or immune criteria.[4] Most of the deaths in 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.[13] Additionally, infants treated early had decreased immune activation, greater recovery of CD4 cells, expanded CD4-naive T-cells, and retention of innate effector frequencies, resulting in greater immune reconstitution than achieved with deferred ART.[14] 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 <12 months regardless of clinical status, CD4 percentage, or viral load (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 younger than 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 infants with HIV; by 12 months, approximately 50% of children develop moderate immune suppression and 20% develop severe immune suppression.[15] In the HIV Paediatric Prognostic Markers Collaborative 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.[16] Unfortunately, although the risk of progression is greatest in the first year of life, the ability to differentiate children at risk of rapid versus slower disease progression by clinical and laboratory parameters is also most limited in young infants. 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.[16]

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.[8,17-19] Several small studies have demonstrated that, despite the very high levels of viral replication in infants with perinatally acquired HIV infection, early initiation of treatment can result in durable viral suppression and normalization of immunologic responses to non-HIV antigens in some infants.[20,21] 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.[22,23] Early initiation of suppressive ART (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 HIV-seronegative; however, a viral reservoir remains present, as demonstrated by viral rebound if ART is stopped.[22,24-26] Although there is a single case report of a period of 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 lymphocytes and other cells.[27-29]

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 3-drug ART regimen at ages 30 hours through 18 months, after which ART was discontinued against medical advice. Intensive follow-up evaluations showed no evidence of virologic rebound for more than 2 years following discontinuation of ART, after which time viremia recurred and ART was restarted.[30,31] This experience has prompted increasing support for initiation of treatment in the first weeks of life, as soon as the diagnosis is made. However, because of limited safety and pharmacokinetic data and experience with ARV drugs in infants <2 to 4 weeks, particularly among premature infants, drug and dose selection in this age group is challenging (see What to Start and Specific Issues in Antiretroviral Treatment for Neonates).[32] If early treatment is initiated, the Panel does not recommend empiric treatment interruption.

Virologic suppression may take longer to achieve in young children than in older children or adults.[33,34] Possible reasons for the slower response in infants include higher virologic set points in young infants, inadequate ARV drug levels, 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 at <12 months.[8,35,36] In a 5-year follow-up study of 40 children with HIV who initiated treatment at <6 months, 98% had CD4 percentage >25% and 78% had undetectable viral load with median follow-up of 5.96 years.[8]

More rapid viral suppression in young infants may be important in reducing the long-lived HIV reservoir. 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.[37-39] Similarly, the Pediatric HIV/AIDS Cohort Study/Adolescent Master Protocol (a cross-sectional study of 144 youth with perinatal HIV with long-term viral suppression) 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).[40]

Information on appropriate drug dosing in infants aged <3 to 6 months, and particularly preterm infants, is limited.[32] Hepatic and renal functions are immature in newborns undergoing rapid maturational changes during the first few months of life, which can result in substantial differences in ARV dose requirements between young infants and older children.[41] 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).

Finally, the possibility of long-term toxicities (e.g., lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, mitochondrial dysfunction) with prolonged therapy is a concern.[42] 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 ≥1 year.[15] However, children with CDC Clinical Stage 3-defining OIs (see Revised Surveillance Case Definition for HIV Infection at http://www.cdc.gov/mmwr/pdf/rr/rr6303.pdf 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 ≥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.[43] ART is also recommended for these children, but because of 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[44] 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.[4,45] 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 Pediatric Randomised Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) multicenter, open-label trial randomized 300 children with HIV aged >1 year (median 6.4 years) to immediate initiation of ART or deferral until the CD4 percentage was <15%.[46] AIDS-free survival at week 144 was 98.7% (95% CI, 94.7–99.7) in the deferred group and 97.9% (CI, 93.7–99.3) in the immediate therapy group ($P = 0.6$), and immediate ART did not significantly improve neurodevelopmental outcomes.[5] However, because of the low event rate, the study was underpowered to detect a difference between the 2 groups. The trial did show better height gain for children who started ART immediately.[46] 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 limited enrollment of children aged <3 years poses restrictions on its value for recommendations in that age group.

In contrast, mortality and growth was evaluated after ART initiation using observational data from 20,756 ART-naive children aged 1 to 16 years at enrollment from 19 cohorts in Europe, Southern Africa, and West Africa, showing a general trend toward lower mortality and better growth with earlier treatment initiation.[6] In children aged <10 years at enrollment, by 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$^3$. The best outcomes were observed in European children who attained growth outcomes comparable to children who were HIV-uninfected. 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.[47-51] In the PENPACT-1 (Pediatric AIDS Clinical Trials Group 390/Paediatric European Network for Treatment of AIDS-9) 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% and 59% of those starting with CD4 percentage 15% to 24% achieved CD4 percentage >25% after 5 years of therapy.[52] Younger age at initiation of therapy has been associated with improved immune response and with more rapid growth reconstitution.[19,20,52,53]

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.[54] Finally, the PREDICT Study demonstrated improved height *z*-scores in the early treatment arm compared with no improvement in the deferred arm.[46] 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.[55-57] Medication adherence is the core requirement for successful virologic control, but achieving consistent adherence in childhood is often challenging.[58] 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.[59]

However, the Panel considers that with increasing evidence of long-term benefits of early ART including reduced mortality in children aged <10 years[6] along with improved growth and pubertal outcomes, improved immune reconstitution and reduced inflammation in children and adolescents, the benefits of early ART initiation outweigh potential risks, and recommend 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.[60] The Panel has formulated recommendations related to the urgency of initiation of ART based on age, clinical status and CD4 cell count (see Box Recommendation). In general, except in infants younger than age 12 months and children with advanced HIV infection, ART does not need to be started urgently (i.e., within 1–2 weeks). Before initiating therapy, it is important to take time 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.

Patients, caregivers, and providers may collaboratively choose to postpone therapy, and on a case-by-case basis, may 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[a] 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 |

[a] The stage is based primarily on the CD4 cell count; the CD4 cell count takes precedence over the CD4 percentage, and the percentage is considered only 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.

**Table 6: HIV-Related Symptoms**

| Mild HIV-Related Symptoms |
|---|
| Children with 2 or more of the conditions listed but none of the conditions listed in Moderate Symptoms category<br>• Lymphadenopathy (≥0.5 cm at more than 2 sites; bilateral at 1 site)<br>• Hepatomegaly<br>• Splenomegaly<br>• Dermatitis<br>• Parotitis<br>• Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media |
| **Moderate HIV-Related Symptoms** |
| • Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count <1,000/µL [<1.0 × $10^9$/L]), and/or thrombocytopenia (platelet count <100 × 103/µL [<100 × $10^9$/L]) persisting for ≥30 days<br>• Bacterial meningitis, pneumonia, or sepsis (single episode)<br>• Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children aged >6 months<br>• Cardiomyopathy<br>• Cytomegalovirus infection, with onset before 1 month<br>• Diarrhea, recurrent or chronic<br>• Hepatitis<br>• Herpes simplex virus (HSV) stomatitis, recurrent (>2 episodes within 1 year)<br>• HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month<br>• Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome<br>• Leiomyosarcoma<br>• Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex<br>• Nephropathy<br>• Nocardiosis<br>• Persistent fever (lasting >1 month)<br>• Toxoplasmosis, onset before 1 month<br>• Varicella, disseminated (complicated chickenpox) |

**Table 6: HIV-Related Symptoms**, page 2 of 2

| **Stage-3-Defining Opportunistic Illnesses in HIV Infection** |
|---|
| • Bacterial infections, multiple or recurrent[a]<br>• Candidiasis of bronchi, trachea, or lungs<br>• Candidiasis of esophagus<br>• Cervical cancer, invasive[b]<br>• Coccidioidomycosis, disseminated or extrapulmonary<br>• Cryptococcosis, extrapulmonary<br>• Cryptosporidiosis, chronic intestinal (>1 month duration)<br>• Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month<br>• Cytomegalovirus retinitis (with loss of vision)<br>• Encephalopathy attributed to HIV[c]<br>• HSV: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)<br>• Histoplasmosis, disseminated or extrapulmonary<br>• Isosporiasis, chronic intestinal (>1 month duration)<br>• Kaposi sarcoma<br>• Lymphoma, Burkitt (or equivalent term)<br>• Lymphoma, immunoblastic (or equivalent term)<br>• Lymphoma, primary, of brain<br>• *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary<br>• *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary<br>• *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary<br>• *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) pneumonia<br>• Pneumonia, recurrent[b]<br>• Progressive multifocal leukoencephalopathy<br>• Salmonella septicemia, recurrent<br>• Toxoplasmosis of brain, onset at age >1 month<br>• Wasting syndrome attributed to HIV[c] |

[a] Only among children aged <6 years.

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

[c] Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references:

- Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*. 1994;43(No. RR-12).
- Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*. 1992;41(No. RR-17).

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 April 27, 2017; last reviewed April 27, 2017)

| Panel's Recommendations |
|---|
| • Selection of an initial regimen should be individualized based on several factors, including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.<br>• For treatment-naive children, the Panel recommends initiating antiretroviral therapy with 3 drugs, including either a boosted protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone **(AI*)**.<br>  • Table 7 provides a list of Panel-recommended regimens that are designated as *Preferred*, *Alternative*, or for use in *Special Circumstances*; recommendations vary by age, weight, and sexual maturity rating. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***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*<br>*† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents* |

## Criteria Used for Recommendations

In general, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel)'s recommendations 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 III clinical trials of antiretroviral therapy (ART) in pediatric patients exist that provide direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic (PK) trials and non-randomized, 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.

Information considered by the Panel for recommending specific drugs or regimens includes:

- 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., 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 several categories as follows:

- *Preferred:* Drugs or drug combinations are designated as *Preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies using surrogate markers demonstrate 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 there are disadvantages compared with preferred regimens in terms of more limited experience in children: 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.
- *Special Circumstances:* Some drugs or drug combinations are recommended for use as initial therapy only in *Special Circumstances* when preferred or alternative drugs cannot be used.

## Factors to Consider When Selecting an Initial Regimen

An ART regimen for children should generally consist of 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus 1 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 lifelong, considerations related to the choice of initial antiretroviral (ARV) regimen should also include an understanding of 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, lamivudine, tenofovir disoproxil fumarate, (TDF) and tenofovir alafenamide (TAF) have antiviral activity and efficacy against hepatitis B and should be considered children with coinfection. For a comprehensive review of this topic, as well as hepatitis C and tuberculosis during HIV coinfection, see the Tuberculosis section of Pediatric OI 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, results of viral drug resistance testing, drug efficacy and AEs, patient and family preference, pill size, and dosing frequency.

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 age of the population studied and specific drug within the class.

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

- Those in the nevirapine group demonstrated greater, but not statistically significant, improvements in immunologic status and growth. Similar improved immune and growth parameters were also demonstrated in the NEVEREST study where children switched to a nevirapine regimen versus those who continued on a LPV/r regimen after achieving virologic control.[2]
- PENPACT-1 (PENTA 9/PACTG 390) compared a PI-based regimen and a NNRTI-based regimen in treatment-naive children aged 30 days to <18 years (the study did not dictate the specific NNRTI or PI 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 efavirenz and 38% received nevirapine. After 4 years of follow-up, 73% of children randomized to PI-based therapy and 70% randomized to NNRTI-based therapy remained on their initial ART regimen. In both groups, 82% of children had viral loads <400 copies/mL.[3]
- The PROMOTE-pediatrics trial demonstrated comparable virologic efficacy among children randomized to receive either an NNRTI or LPV/r-based ART.[4] Children were aged 2 months to <6 years and had no perinatal exposure to nevirapine. Selection of NNRTI was based on age (children aged <3 years received nevirapine and those aged >3 years primarily received efavirenz). At 48 weeks, the proportion with HIV RNA level <400 copies/mL at 48 weeks was 80% in the LPV/r arm versus 76% in the NNRTI arm, a difference of 4% and not statistically significant (95% CI: -9% to +17%).

Clinical investigation of INSTI-based regimens in children has been limited to non-comparative 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 showing superior efficacy of INSTI-containing compared to PI-containing and NNRTI-containing regimens[5,6] and small studies in ART-naive adolescents.[7]

Based on the above data, the Panel considers the following as *Preferred* for children when used in combination with 2 NRTIs:

- Aged <14 days: Nevirapine
- Aged ≥14 days to <2 years: LPV/r
- Aged ≥2 years to <3 years: LPV/r or raltegravir
- Aged ≥3 to <6 years: Raltegravir, boosted atazanavir, or twice-daily boosted darunavir
- Aged ≥6 to <12 years: Dolutegravir (body weight ≥30 kg) or boosted atazanavir
- Aged ≥12 years or body weight as noted for children who have not reached sexual maturity:
  - Weighing ≥30 kg: Dolutegravir
  - Weighing ≥35 kg: Elvitegravir/cobicistat (only the elvitegravir/cobicistat-containing fixed-drug combination elvitegravir/cobicistat/emtricitabine/TAF is recommended at this time)
  - Weighing ≥40 kg: Boosted atazanavir or once-daily boosted darunavir

*Alternative* and *Special Circumstances* regimens are shown in Table 7.

## Integrase Strand Transfer Inhibitor-Based Regimens

Three INSTIs—dolutegravir, elvitegravir, and raltegravir—are licensed for the treatment of ARV-naive 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. Raltegravir is licensed for treatment of children as young as age 4 weeks. Dolutegravir is approved for use in children weighing ≥30 kg. Elvitegravir has been studied in adolescents in 2 fixed-dose combination regimens and in combination with 2 NRTIs and ritonavir 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 dolutegravir for use in children weighing ≥30 kg. The approval was supported by data from a study of 46 treatment-experienced—but INSTI-naive—adolescents[7,8] and 11 treatment-experienced (but INSTI-naive) children aged ≥6 years.[9] The drug has a very favorable safety profile and can be given once daily in treatment of INSTI-naive patients.

Recommendation:

- Based on virologic potency and safety profile in adult and pediatric studies,[5,7,10] the Panel recommends dolutegravir in combination with a 2-NRTI backbone as a *Preferred* INSTI regimen for children and adolescents weighing ≥30 kg **(AI*)**.

### Elvitegravir

Elvitegravir is an INSTI available as a tablet, as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TDF and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TAF. Both are FDA-approved for use in ART-naive adults with HIV. Elvitegravir/cobicistat/emtricitabine/TAF is FDA-approved for use in ART-naive adolescents aged ≥12 years and weighing ≥35 kg. Cobicistat is a specific, potent cytochrome P3A (CYP3A) inhibitor that has no activity against HIV and is used as a PK enhancer, which allows for once-daily dosing of elvitegravir.

Recommendation:

- Based on virologic potency and safety profile in adult and adolescent studies,[11-15] the Panel recommends elvitegravir only in the fixed-dose combination elvitegravir/cobicistat/emtricitabine/TAF as a *Preferred* INSTI regimen for children and adolescents aged ≥12 years and weighing ≥35 kg **(AI*)**.

### Raltegravir

Raltegravir is FDA-approved for treatment of children aged ≥4 weeks and weighing ≥3 kg. It is available in film-coated tablets, chewable tablets, and single packets of granules for oral suspension.

Recommendation:

- Based on randomized clinical trials in adults and pediatric studies, largely in ARV-experienced children and adolescents,[5,16-22] the Panel recommends raltegravir as a *Preferred* INSTI in children aged ≥2 years to <6 years who are able to take either the chewable or film-coated tablets.
- Raltegravir is an *Alternative* INSTI for children and adolescents aged ≥6 years, because of the availability of once-daily regimens with other drugs.
- At this time, there is limited information about the use of single packets of granules for oral suspension in children aged <2 years. Because of the limited data, the Panel recommends raltegravir granules as an *Alternative* INSTI in children aged ≥4 weeks to <2 years.

## Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Efavirenz (aged ≥3 months), etravirine (aged ≥6 years), nevirapine (aged ≥15 days), and rilpivirine (aged ≥12 years) have an FDA-approved pediatric indication for treatment of HIV infection. Advantages of NNRTIs as initial therapy include long half-life allowing for less frequent drug administration, lower risk of dyslipidemia and fat maldistribution compared to some agents in the PI class, and generally, compared to PIs, a lower pill burden. The major disadvantages of NNRTI drugs FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance (except etravirine) 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 is most frequent with nevirapine, at least in adults with HIV. NNRTIs have the potential to interact with other drugs 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 on each drug).

### Efavirenz

Efavirenz in combination with 2 NRTIs is the *Preferred* NNRTI for initial therapy of children aged ≥3 to 12 years based on clinical trial experience in adults and children. Efavirenz capsules can be opened and sprinkled on age-appropriate food for use in children aged 3 months weighing ≥3.5 kg.[23] However, because of concerns regarding variable PK of the drug in the very young, the Panel does not currently endorse its use for infants and children aged 3 months to 3 years.

Recommendation:

- Based on efficacy and tolerability,[10,16,23-41] the Panel recommends efavirenz in combination with a 2-NRTI backbone as the *Alternative* NNRTI regimen for initial treatment of HIV in children aged ≥3 **(AI*)**.

### Nevirapine

Nevirapine has extensive clinical and safety experience in children with HIV and has shown ARV efficacy in a variety of combination regimens.[1,3,4,42-46] Nevirapine has also been used extensively as prophylaxis for the prevention of HIV transmission in young infants in the peripartum period and during breastfeeding. Although there is information about the safety and pharmacokinetics of nevirapine used at prophylaxis doses that target lower nevirapine drug levels, there is less information regarding higher doses necessary for treatment. Early testing of infants allows identification of confirmed HIV infection before 14 days of age. In these cases, the Panel recommends the use of nevirapine 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 nevirapine in infants aged <14 days of can be located in Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection.

Recommendation:

- Based on the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare (but potentially life-threatening) hepatitis,[47,48] and conflicting data about virologic efficacy compared to preferred regimens,[1,3,4,44-46,49-57] the Panel recommends nevirapine in combination with a 2-NRTI backbone as a *Preferred* NNRTI regimen in infants aged <14 days and an *Alternative* NNRTI regimen for children aged ≥14 days to <3 years **(AI)**. A change from nevirapine to LPV/r should be considered after 14 days of life and 42 weeks post-gestational age based on infant genotype and the better outcomes of LPV/r in children aged <3 years.

### Rilpivirine

Rilpivirine is currently available both as a single-agent formulation and a once-daily, fixed-dose combination tablet containing emtricitabine and TDF. The single-agent formulation is approved for use in adolescents aged ≥12 years.

Recommendation:

- Based on the limited experience in adolescents and larger body of evidence in adults,[31,58-62] the Panel recommends rilpivirine in combination with a 2-NRTI backbone as an *Alternative* NNRTI regimen for children and adolescents aged ≥12 years and weighing ≥35 kg and with HIV viral load ≤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 (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 in selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly 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.

Ritonavir is a potent inhibitor of the cytochrome P450 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 ritonavir is used as a PI booster with other PIs, 2 agents must be administered. In addition, the use of ritonavir boosting increases the potential for hyperlipidemia[63] and drug-drug interactions.

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

### Atazanavir/Ritonavir

Atazanavir is a once-daily PI that was approved by the FDA in March 2008 for use in combination with a 2-NRTI backbone in children aged ≥6 years. Atazanavir is most often boosted with ritonavir. Approval was extended in 2014 for use in infants and children aged ≥3 months and weighing ≥5 kg. Atazanavir in combination with cobicistat has been approved by the FDA for use in adults. Its use in children and adolescents is under investigation but no data are currently available.

Recommendation:

- Based on virologic potency in adult and pediatric studies and tolerability in pediatric studies,[19,27,60,63-69] the Panel recommends atazanavir/ritonavir (ATV/r) in combination with a 2-NRTI backbone as a *Preferred* PI regimen for children aged ≥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 atazanavir.

### Darunavir/Ritonavir

Darunavir/ritonavir (DRV/r) is FDA-approved for ARV-naive and ARV-experienced adults and for ARV-naive and ARV-experienced children aged ≥3 years. DRV/r is approved for once-daily use in adults and children without darunavir resistance-associated mutations. Once-daily dosing of DRV/r was conducted as a sub-study of a twice-daily dosing trial in children aged 3 to <12 years. This PK evaluation lasted only 2 weeks, after which the participants switched back to the twice-daily regimen.[70] 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-naive or treatment-experienced children aged <12 years, the Panel recommends dosing darunavir with ritonavir twice daily in children aged >3 years to <12 years.[71]

Recommendation:

- Based on its virologic potency in adult and pediatric studies, high barrier to development of drug resistance, and excellent toxicity profile in adults and children,[19,71-78] the Panel recommends DRV/r in combination with a 2-NRTI backbone as a *Preferred* PI regimen for children aged ≥3 years to <6 years and children and adolescents aged ≥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-naive children and adolescents weighing ≥40 kg **(AI*)**.

- Twice-daily dosing of DRV/r is part of a *Preferred* PI regimen in children aged ≥3 to <6 years and weighing ≥10 kg and an *Alternative* PI regimen in children aged ≥6 years to <12 years **(AI*)**.
- Twice-daily dosing of DRV/r if the following darunavir resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

**Lopinavir/Ritonavir**

Lopinavir/ritonavir (LPV/r) is approved for treatment of HIV infection in adults and in infants and children with a postmenstrual age ≥42 weeks and postnatal age ≥14 days. Once-daily LPV/r is FDA-approved for initial therapy in adults,[79] but PK data in children do not support a recommendation for once-daily dosing.[80-82]

Recommendation:

- Based on virologic potency in adult and pediatric studies and tolerability in pediatric studies,[10,29,64,65,72,79-81,83-87] the Panel recommends LPV/r in combination with a 2-NRTI backbone as a *Preferred* PI regimen for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days to <3 years **(AI)**.

## 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, 8 NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, TDF, and TAF) are FDA-approved for use in children aged <13 years. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; emtricitabine in combination with stavudine or didanosine; TDF in combination with lamivudine or emtricitabine; and TAF in combination with emtricitabine.[15,37,66,88-92] Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 8. Also, see Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

In the dual-NRTI regimens listed below, lamivudine and emtricitabine are interchangeable. Both lamivudine and emtricitabine are well tolerated with few AEs. Although there is less experience in children with emtricitabine than with lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir or TDF or zidovudine). The main advantage of emtricitabine over lamivudine is that it can be administered once-daily as part of an initial regimen. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine, and improved susceptibility to zidovudine, stavudine, and TDF based on decreased viral fitness.[93,94]

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

**Abacavir in Combination with Lamivudine or Emtricitabine**

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

Recommendations:

- Based on virologic efficacy and favorable toxicity profile,[17,95-102] the Panel recommends abacavir plus lamivudine or emtricitabine as the *Preferred* dual-NRTI combination for children aged ≥3 months **(AI)**.
- Once-daily doing of abacavir is recommended when using the pill formulation. Twice-daily dosing of liquid abacavir is recommended for initial therapy; a change to once-daily dosing can be considered in clinically stable patients with undetectable viral load and stable CD4 cell count after approximately 6 months (24 weeks) of twice-daily dosing.[103-106]

### 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-drug combination tablet also containing elvitegravir, cobicistat, and emtricitabine for the treatment of HIV in ARV-naive individuals aged ≥12 years with estimated creatinine clearance ≥30 mL/min.

Recommendation:

- Based on the potential for less renal and bone AEs,[13,107] the Panel recommends TAF plus emtricitabine (combined with elvitegravir and cobicistat) as a *Preferred* dual-NRTI combination in children and adolescents weighing ≥35 kg with estimated creatinine clearance ≥30 mL/min.

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

TDF is FDA-approved for use in children and adolescents aged ≥2 years when administered as part of an ART regimen.

Recommendation:

- Based on virologic efficacy and ease of dosing,[89-92,96-99,108-113] the Panel recommends TDF in combination with lamivudine or emtricitabine as an *Alternative* dual-NRTI combination for use in children and adolescents at Sexual Maturity Rating (SMR) III **(AI*)**.
- Because of decreases in bone mineral density (BMD) observed in adults and children receiving TDF and its unknown clinical significance,[89-92,114,115] the Panel recommends TDF use in children aged ≥2 years and SMR I or II in *Special Circumstances* after weighing potential risks of decreased BMD versus benefits of therapy.

### Zidovudine in Combination with Lamivudine or Emtricitabine

Zidovudine is available as a syrup, capsule, tablet, and injectable/intravenous preparations. It is licensed for treatment in infants as young as 4 weeks and prophylaxis in newborns.

Recommendation:

- Because of the extensive experience and favorable safety profile,[100,116-118] the Panel recommends zidovudine in combination with lamivudine or emtricitabine as a *Preferred* NRTI for infants and children from birth to ≤12 years **(AI*)**.
- In adolescents, the Panel recommends zidovudine in combination with lamivudine or emtricitabine as an *Alternative* NRTI because zidovudine 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 as alternative dual-NRTI combinations:

### Zidovudine in Combination with Abacavir or Didanosine (BII)

- In a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities.[116]
- Zidovudine plus abacavir and zidovudine plus lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir plus lamivudine in a European pediatric study.[88,95]

### Didanosine in Combination with Lamivudine or Emtricitabine (BI*)

- The combination of didanosine and emtricitabine allows for once-daily dosing.[37]
- Didanosine is recommended to be administered on an empty stomach but that is impractical for infants who must be fed frequently and it may decrease medication adherence in older children because of the complexity of the regimen.

- To improve adherence, some practitioners recommend administration of didanosine to young children without regard to timing of meals. However, data are inadequate to allow a strong recommendation at this time, and it is preferable to administer didanosine under fasting conditions when possible.

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

An ART regimen in treatment-naive children generally contains 1 NNRTI **or** 1 PI boosted with ritonavir **or** cobicistat or 1 INSTI **plus** a 2-NRTI backbone. Preferred regimens are so designated based on efficacy, ease of administration and acceptable toxicity. Alternative regimens have also demonstrated efficacy, but have disadvantages compared with preferred regimens in terms of more limited experience in children or less favorable ease of administration. Regimens should be individualized based on advantages and disadvantages of each combination (see Table 8).

For children who are receiving an effective and tolerable ART regimen, that regimen can be continued as they age even if the combination they are receiving is no longer a preferred regimen.

| | |
|---|---|
| **Preferred Regimens** | |
| Infants, Birth to <14 Days[a,b] | 2 NRTIs **plus** NVP |
| Children Aged ≥14 Days to <2 Years | 2 NRTIs **plus** LPV/r |
| Children Aged ≥2 Years to <3 Years | 2 NRTIs **plus** LPV/r |
| | 2 NRTIs **plus** RAL[c] |
| Children Aged ≥3 Years to <6 Years | 2 NRTIs **plus** ATV/r |
| | 2 NRTIs **plus** twice-daily DRV/r[d] |
| | 2 NRTIs **plus** RAL[c] |
| Children Aged ≥6 Years to <12 Years | 2 NRTIs **plus** ATV/r |
| | 2 NRTIs **plus** DTG[e] |
| Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III) | 2 NRTIs **plus** ATV/r |
| | 2 NRTIs **plus** DTG[e] |
| | 2 NRTIs **plus** once-daily DRV/r[d] |
| | 2 NRTIs **plus** EVG/COBI[f] |
| Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V) | Refer to Adult and Adolescent Guidelines |
| **Alternative Regimens** | |
| Children Aged >14 Days to <3 Years | 2 NRTIs **plus** NVP[g] |
| Children Aged ≥4 Weeks to <2 Years and Weighing ≥3 kg | 2 NRTIs **plus** RAL[c] |
| Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg | 2 NRTIs **plus** ATV/r |
| Children Aged ≥3 Years to <6 Years | 2 NRTIs **plus** EFV[h] |
| | 2 NRTIs **plus** LPV/r |
| Children Aged ≥6 Years to <12 Years | 2 NRTIs **plus** twice-daily DRV/r[d] |
| | 2 NRTIs **plus** EFV[h] |
| | 2 NRTIs **plus** LPV/r |
| | 2 NRTIs **plus** RAL[c] |
| Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III) | 2 NRTIs **plus** EFV[h] |
| | 2 NRTIs **plus** RAL[c] |
| | 2 NRTIs **plus** RPV[i] |
| **Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs** | |
| Children, Birth to <3 Months | ZDV **plus** (3TC **or** FTC) |

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

| **Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs**, continued | |
|---|---|
| Children Aged ≥3 Months to <12 Years | ABC **plus** (3TC **or** FTC) |
| | ZDV **plus** (3TC **or** FTC) |
| Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III) | ABC **plus** (3TC **or** FTC) |
| | TAF **plus** FTC |
| Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V) | Refer to the Adult and Adolescent Guidelines |
| **Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs** | |
| Children Aged ≥2 Weeks | ZDV **plus** ddI |
| Children Aged ≥3 Months | ZDV **plus** ABC |
| Adolescents at SMR III | TDF **plus** (3TC **or** FTC) |
| Adolescents Aged ≥12 Years at SMR III | ZDV **plus** (3TC **or** FTC) |
| **2-NRTI Regimens for Use in Special Circumstances in Combination with Additional Drugs** | |
| Children Aged ≥2 Years and Adolescents, SMR I or II | ddI **plus** (3TC **or** FTC) |
| | TDF **plus** (3TC **or** FTC) |

[a] If treatment initiation is planned prior to 14 days of age, NVP is the *Preferred* agent. 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). 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 located in Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection. A change from NVP to LPV/r should be considered when the infant is aged ≥14 days and 42 weeks post-gestational age, based on infant genotype and the better outcomes of LPV/r in children aged <3 years.

[b] LPV/r should 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 postnatal age ≥14 days.

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children aged 4 weeks to 2 years.

[d] DRV once-daily should not be used in children aged <12 years or weighing <40 kg or 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 and not sexually mature (SMR I–III) where once-daily administration is possible.

[e] DTG is recommended only for children and adolescents weighing ≥30 kg.

[f] EVG is currently recommended only in fixed-dose combination tablets. Tablets containing EVG/COBI/FTC/TAF are recommended as *Preferred* for children and adolescents weighing ≥35 kg. Tablets containing EVG/COBI/FTC/TDF are recommended only for children and adolescents weighing ≥35 kg, and in SMR IV or V.

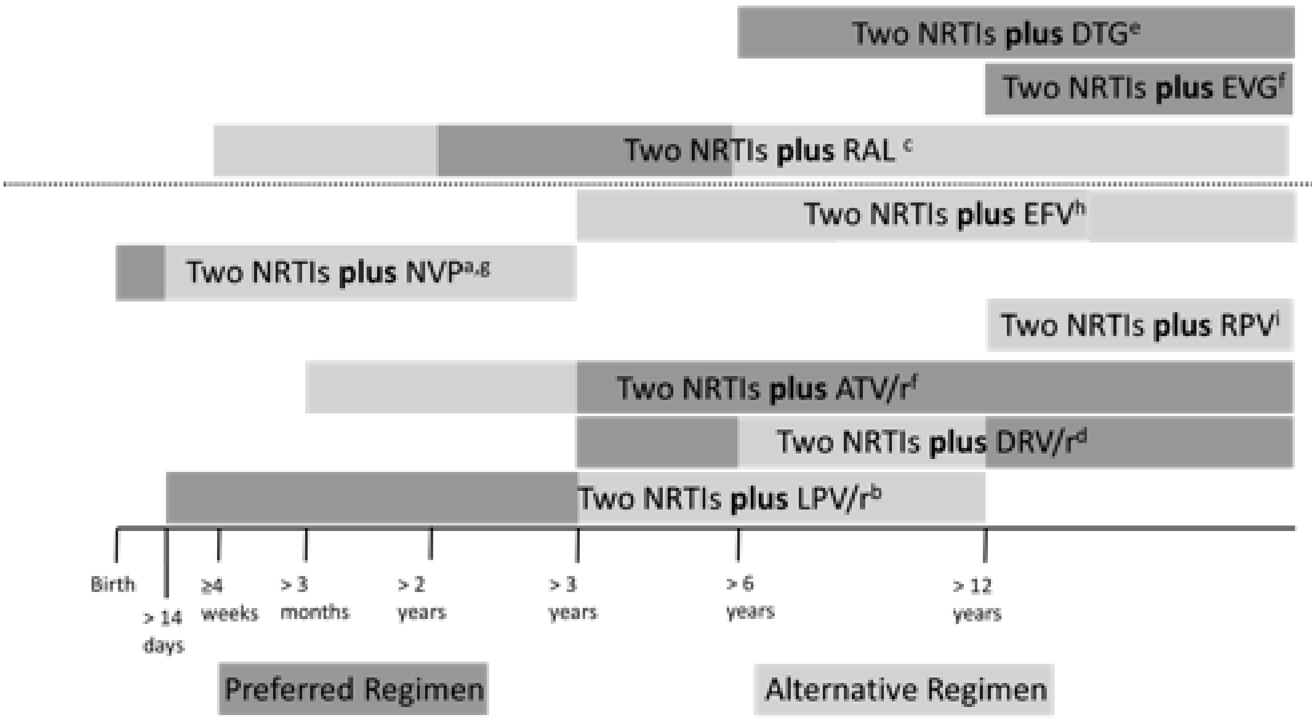
[g] NVP should not be used in post-pubertal girls with a CD4 cell count >250/mm$^3$, unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged ≥15 days.

[h] ERV is licensed for use in children aged ≥3 months who weigh ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years.

[i] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; COBI=cobicistat; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FDA = Food and Drug Administration; 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; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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




[a] If treatment initiation is planned prior to 14 days of age, NVP is the *Preferred* agent. 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). 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 located in Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection. 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 year.

[b] LPV/r should 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 postnatal age ≥14 days.

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children aged 4 weeks to 2 years.

[d] DRV once-daily should not be used in children aged <12 years or weighing <40 kg and 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 and not sexually mature (SMR I–III) where once-daily administration is possible.

[e] DTG is recommended only for children and adolescents weighing ≥30 kg.

[f] EVG is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir plus cobicistat plus emtricitabine plus TAF are recommended as *Preferred* for children and adolescents weighing ≥35 kg. Tablets containing elvitegravir plus cobicistat plus emtricitabine plus TDF are recommended only for children and adolescents weighing ≥35 kg, and in SMR IV or V.

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

[h] EFV is licensed for use in children aged ≥3 months who weigh ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years.

[i] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

**Key to Acronyms:** ATV/r = atazanavir/ritonavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG=elvitegravir; FDA = Food and Drug Administration; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RAL = raltegravir; RPV=rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

**Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a]** (page 1 of 4)

| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **INSTIs**<br>In Alphabetical Order | | Integrase Inhibitor Class Advantages:<br>• Susceptibility of HIV to a new class of ARV drugs<br>• Few drug-drug interactions<br>• Well-tolerated | Integrase Inhibitor Class Disadvantages:<br>• Limited data on pediatric dosing or safety |
| | DTG | • Once-daily administration<br>• Can give with food<br>• Available as a fixed-dose combination tablet containing ABC/3TC/DTG (Triumeq) in a single, but large, tablet<br>• Single-agent DTG pills are available in several dosages and are small in size | • Drug interactions with EFV, FPV/r, TPV/r, and rifampin necessitating twice-daily dosing |
| | EVG | • Once-daily administration<br>• Available as a fixed-dose combination tablet containing EVG/COBI/FTC/TDF (Stribild) and as a fixed-dose combination tablet containing EVG/COBI/FTC/TAF (Genvoya) | • COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4)<br>• COBI inhibits tubular secretion of creatinine and may result in increased serum creatinine but with normal glomerular clearance. |
| | RAL | • Can give with food.<br>• Available in tablet, chewable tablet, and powder formulations | • Potential for rare systemic allergic reaction or hepatitis |
| **NNRTIs**<br>In Alphabetical Order | | NNRTI Class Advantages:<br>• Long half-life<br>• Less dyslipidemia and fat maldistribution than PIs<br>• PI-sparing<br>• Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens. | NNRTI Class Disadvantages:<br>• Single mutation can confer resistance, with cross-resistance between EFV and NVP.<br>• Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP)<br>• Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4). |
| | EFV | • Once-daily administration<br>• Available as a fixed-dose combination tablet containing EFV/FTC/TDF (Atripla)<br>• Potent ARV activity<br>• Can give with food (but avoid high-fat meals).<br>• Capsules can be opened and added to food. | • Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects)<br>• Rash (generally mild)<br>• No commercially available liquid.<br>• Limited data on dosing for children aged <3 years.<br>• No data on dosing for children aged <3 months.<br>• Use with caution in adolescent females of childbearing age. |
| | NVP | • Liquid formulation available.<br>• Dosing information for young infants available.<br>• Can give with food<br>• Extended-release formulation is available that allows for once-daily dosing in older children. | • Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen.<br>• Higher incidence of rash/HSR than other NNRTIs<br>• Higher rates of serious hepatic toxicity than EFV<br>• Decreased virologic response compared with EFV<br>• Twice-daily dosing necessary in children with BSA $<0.58\ m^2$ |

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

| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **NNRTIs**<br>In Alphabetical Order | RPV | • Once-daily dosing<br>• Available in a 1-pill-daily, fixed-dose combination tablet containing RPV/FTC/TDF (Complera) and RPV/FTC/TAF (Odefsey) | • Should not use in patients with HIV viral load >100,000 copies/mL<br>• Low barrier for resistance |
| **PIs**<br>In Alphabetical Order | | <u>PI Class Advantages</u>:<br>• NNRTI-sparing<br>• Clinical, virologic, and immunologic efficacy are well-documented.<br>• Resistance to PIs requires multiple mutations.<br>• When combined with dual-NRTI backbone, targets HIV at 2 steps of viral replication (viral reverse transcriptase and protease enzymes). | <u>PI Class Disadvantages</u>:<br>• Metabolic complications, including dyslipidemia, fat maldistribution, insulin resistance<br>• Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4)<br>• Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations<br>• Poor palatability of liquid preparations, which may affect adherence to treatment regimen<br>• Most PIs require ritonavir boosting resulting in associated drug interactions. |
| | ATV/r | • Once-daily dosing<br>• Powder formulation available<br>• ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters).<br>• Available in a fixed-dose combination tablet containing ATV/COBI (Evotaz) that reduces pill burden of a boosted PI regimen | • No liquid formulation<br>• Food effect (should be administered with food)<br>• Indirect hyperbilirubinemia is common but asymptomatic.<br>• Must be used with caution in patients with preexisting conduction system defects (can prolong PR interval of ECG).<br>• RTV component associated with large number of drug interactions. |
| | DRV/r | • Can be used once daily in children aged ≥12 years<br>• Liquid formulation available<br>• Available in a fixed-dose combination tablet containing DRV/COBI (Prezcobix) that reduces pill burden of a boosted PI regimen. | • Pediatric pill burden high with current tablet dose formulations<br>• Food effect (should be administered with food)<br>• Must be given with RTV boosting to achieve adequate plasma concentrations.<br>• Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown.<br>• RTV component associated with large number of drug interactions.<br>• Can only be used once-daily in absence of certain PI-associated resistance mutations. |
| | LPV/r | • LPV only available coformulated with RTV in liquid and tablet formulations.<br>• Tablets can be given without regard to food but may be better tolerated when taken with meal or snack. | • Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone.<br>• Food effect (liquid formulation should be administered with food).<br>• RTV component associated with large number of drug interactions.<br>• Should 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 ≥14 days.<br>• Must be used with caution in patients with preexisting conduction system defects (can prolong PR and QT interval of ECG). |

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

| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **Dual-NRTI Backbones**<br>In Alphabetical Order | ABC **plus** (3TC **or** FTC) | • Palatable liquid formulations<br>• Can give with food.<br>• ABC and 3TC are coformulated as a single pill for older/larger patients weighing ≥25 kg<br>• Available as a fixed-dose combination tablet containing ABC/3TC/DTG (Triumeq) in a single, but large, tablet. | • Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment. |
| | ddI **plus** (3TC **or** FTC) | • Delayed-release capsules of ddI may allow once-daily dosing in children aged ≥6 years, weighing ≥20 kg, able to swallow pills, and who can receive adult dosing along with once-daily FTC.<br>• FTC available as a palatable liquid formulation administered once daily. | • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be co-administered with FTC or 3TC).<br>• Limited pediatric experience using delayed-release ddI capsules in younger children<br>• Pancreatitis, lactic acidosis, neurotoxicity with ddI |
| | TAF **plus** FTC for adolescents ≥12 years | • Once-daily dosing<br>• Small tablet size<br>• Less tenofovir-associated renal and bone toxicity with TAF compared to TDF in adults<br>• TAF and FTC are coformulated as a single tablet (Descovy).<br>• Available as fixed-dose combination tablets: EVG/COBI/FTC/TAF (Genvoya) and RPV/FTC/TAF (Odefsey) | N/A |
| | TDF **plus** (3TC **or** FTC) for adolescents, SMR IV or V | • Once-daily dosing for TDF<br>• Resistance is slow to develop.<br>• Less mitochondrial toxicity than other NRTIs.<br>• Can give with food.<br>• Available as reduced-strength tablets and oral powder for use in younger children<br>• TDF and FTC are coformulated as single tablet (Truvada) and available in multiple strengths.<br>• Available as fixed-dose combination tablets: EFV/FTC/TDF (Atripla), EVG/COBI/FTC/TDF (Stribild), and RPV/FTC/TDF (Complera) | • Limited pediatric experience<br>• Potential bone and renal toxicity, toxicity may be less in post-pubertal children.<br>• Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV. |
| | ZDV **plus** (3TC **or** FTC) | • Extensive pediatric experience<br>• ZDV and 3TC are coformulated as single pill for older/larger patients.<br>• Palatable liquid formulations<br>• Can give with food.<br>• FTC is available as a palatable liquid formulation administered once daily. | • Bone marrow suppression with ZDV<br>• Lipoatrophy with ZDV |
| | ZDV **plus** ABC | • Palatable liquid formulations<br>• Can give with food. | • Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment<br>• Bone marrow suppression and lipoatrophy with ZDV |

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

| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **Dual-NRTI Backbones**<br>In Alphabetical Order | ZDV **plus** ddI | • Extensive pediatric experience<br>• Delayed-release capsules of ddI may allow SMR dosing of ddI in older children able to swallow pills and who can receive adult doses | • Bone marrow suppression and lipoatrophy with ZDV<br>• Pancreatitis, neurotoxicity, lactic acidosis with ddI<br>• ddI liquid formulation is less palatable than 3TC or FTC liquid formulation<br>• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue. |

[a] See Appendix A: Pediatric Antiretroviral Drug Information and Table 7. Antiretroviral Regimen Considerations as Initial Therapy based on Specific Clinical Scenarios in the Adult ARV Guidelines for more information.

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; AE = adverse event; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; DRV/r = darunavir/ritonavir; ddI = didanosine; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG = elvitegravir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; 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 April 27, 2017; last reviewed April 27, 2017)

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 for consideration in management of 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) in 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 treatment-naive adolescents aged ≥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/$m^2$ basis) are required in adolescents than in adults to achieve adequate drug concentrations.[1] The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend 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 ≥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, has been investigated in children both with and without ritonavir boosting, and was approved by the FDA in June 2007 for use in pediatric patients aged ≥2 years.[2-5] Fosamprenavir-containing regimens are not recommended for initial therapy because of the volume of liquid medication when administered in the suspension form in young children without ritonavir boosting and associated vomiting, and availability of more advantageous boosted-protease inhibitor (PI) agents. 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.[6-9] Therefore, indinavir 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.[10] 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 showing inferior potency of nelfinavir compared with ritonavir-boosted PIs, integrase strand transfer inhibitors (INSTIs), and efavirenz make nelfinavir an agent not recommended for children who are initiating therapy.

### 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.[11,12] 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.[13,14] In a study 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 a viral load of <400 copies/mL at 48 weeks of treatment.[15] 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 infection 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.[16]

### Regimens Containing Three Drug Classes

Data are insufficient to recommend initial regimens containing agents from 3 drug classes (e.g., NRTI plus NNRTI plus PI or INSTI plus NRTI plus PI/NNRTI). Although studies containing 3 classes of drugs have demonstrated these regimens to be 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 3 drug classes, which could severely limit future treatment options.[17-21] Ongoing studies, however, are investigating 3 drug classes as treatment in neonates.

### Regimens Containing Three NRTIs and an NNRTI

Data are currently insufficient to recommend a regimen of 3 NRTIs plus an NNRTI in young infants. A recent review of 9 cohorts from 13 European countries suggested superior responses to this 4-drug regimen when compared to boosted PI or 3-drug NRTI regimens.[22] There has been speculation that poor tolerance and 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 a standard NNRTI-based 3-drug regimen versus a 4-drug regimen (3 NRTIs and 1 NNRTI). After a 36-week induction period, the children on the 4-drug regimen were continued on a dual NRTI plus NNRTI or an all NRTI-based regimen. Although early benefits in CD4 T lymphocyte (CD4) improvement and virologic control were observed in the 4-drug arm, these benefits were not sustained after de-intensification to the 3-NRTI arm.[23] Furthermore, after a median of 3.7 years on therapy, children in the initial 4-drug arm who changed to an all NRTI-based regimen had significantly poorer virologic control.[24] Based on demonstrated benefits of recommended 3-drug regimens and lack of additional efficacy data on the 4-drug regimen, the Panel does not currently recommend this regimen.

### Ritonavir-Boosted Saquinavir

A saquinavir/ritonavir-based regimen compared with a LPV/r-based regimen demonstrated comparable virologic and immunologic outcomes when used as initial therapy in treatment-naive adults.[25] 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.

### Stavudine-Containing Regimens

Stavudine-containing regimens, including the dual-NRTI combination of stavudine/didanosine, are not recommended for use as initial therapy because of greater toxicity compared to other available NRTI combinations. In pediatric studies, stavudine-containing regimens demonstrated virologic efficacy and were well tolerated.[26-29] However, in studies in adults, stavudine with and without didanosine was associated with greater toxicity.[30,31] In addition, the combination of stavudine/didanosine has been linked with cases of fatal and nonfatal lactic acidosis with pancreatitis/hepatic steatosis in women receiving this combination during pregnancy.[32,33]

### Tipranavir-Based Regimens

This agent has been studied in treatment-experienced children and adults. Tipranavir is a PI licensed for use in children aged ≥2 years. Tipranavir-based regimens are not recommended because higher doses of ritonavir to boost tipranavir must be used 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. These agents include elvitegravir (INSTI), and etravirine (NNRTI). 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 be considered as recommended agents or regimens. These are summarized below and are also listed in Table 9.

### Darunavir with Low-Dose Ritonavir When Administered Once Daily (for Children Aged ≥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 now FDA-approved, the Panel is concerned about the lack of efficacy data for individuals aged ≥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 ≥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 enhance ease of use and support adherence if no darunavir-associated resistance mutations are present.

### Efavirenz for Children Aged ≥3 Months to 3 Years

Efavirenz is FDA-approved for use in children as young as 3 months who weigh at least 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). Based on the recommended efavirenz dosage for children aged <3 years, the IMPAACT P1070 study estimated the variability in area under the curve (AUC) for efavirenz based on polymorphisms in cytochrome P (CYP) 2B6 516. The findings suggest that 38% of extensive metabolizers would have sub-therapeutic AUCs and 67% of poor metabolizers would have excessive AUCs based on recommended dosing.[34] Thus, should efavirenz be considered, CYP2B6 genotyping that predicts efavirenz metabolic rate should be performed, if available. Therapeutic drug monitoring can also be considered.

#### Elvitegravir-Based Regimens for Children Aged <12 Years

Elvitegravir is an INSTI available as a tablet and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TDF (Stribild) and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) (Genvoya). All are FDA-approved for use as ART in ART-naive adults with HIV-1 infection. Elvitegravir/cobicistat/emtricitabine/TAF is FDA-approved for use in ART-naive children and adolescents aged ≥12 years and weighing ≥35 kg. Elvitegravir tablets must be taken in combination with a low-dose ritonavir-boosted PI. A small study (14 participants) of Stribild in treatment-naive children and adolescents aged 12 to 17 years has reported PK, tolerability, and virologic efficacy at 24 weeks. The therapy was well tolerated, steady state exposure was similar to adults and, at 24 weeks, all subjects had viral loads <400 copies/mL; 11 had viral loads <50 copies/mL. Elvitegravir/cobicistat/emtricitabine/TAF was studied in 49 ART-naive children and adolescents aged ≥12 years and weighing ≥35 kg and demonstrated PK parameters similar to those for the combination in adults, was well tolerated and, at week 24, all subjects had viral loads <50 copies/mL.[35] Tablets containing elvitegravir/cobicistat/emtricitabine/TAF are recommended as "preferred" for children aged ≥12 years and weighing ≥35 kg. Tablets containing elvitegravir/cobicistat/emtricitabine/TDF are recommended only for adolescents aged ≥12 years and weighing ≥35 kg and in sexual maturity stage 4 or 5 (see What to Start). However, data are insufficient to recommend elvitegravir as part of an initial regimen for children aged <12 years.

#### Etravirine-Based Regimens

Etravirine is an NNRTI that has been studied in treatment-experienced children aged ≥6 years.[36,37] 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 ≥2 years and weighing ≥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 4 age cohorts using both liquid and tablet formulations. Initial dose is based on body surface area and scaled from recommended adult dosage. Dose adjustments were required in patients not receiving a potent CYP450 3A4 inhibitor or inducer.[38] 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-drug combinations so that patients do not inadvertently receive a double dose of a drug contained in such a combination.

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

| Regimen or ARV Component | Rationale for Being Not Recommended |
|---|---|
| Unboosted **ATV**-containing regimens in children | Reduced exposure |
| **DRV**-based regimens once daily in children ≥3 to 12 years | Insufficient data to recommend |
| Unboosted **DRV** | Use without ritonavir has not been studied |
| Dual (full-dose) PI regimens | Insufficient data to recommend<br>Potential for added toxicities |
| Dual NRTI combination of **ABC plus ddI** | Insufficient data to recommend |
| Dual NRTI combination of **ABC plus TDF** | Insufficient data to recommend |
| Regimens containing **d4T** | Increased toxicities |
| Dual NRTI combination of **TDF plus ddI** | Increase in concentrations; high rate of virologic failure |
| **EFV**-based regimens for children aged <3 years | Appropriate dose not determined |
| **T20**-containing regimens | Insufficient data to recommend<br>Injectable preparation |
| **ETR**-based regimens | Insufficient data to recommend |
| **EVG**-based regimens | Insufficient data to recommend regimens containing EVG except when administered as the fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TAF (Genvoya) in adolescents aged 12–18 and weighing ≥35 kg (see What to Start ) |
| **FPV**-based regimens | Reduced exposure<br>Medication burden |
| **IDV**-based regimens | Renal toxicities |
| **LPV/r** dosed once daily | Reduced drug exposure |
| **MVC**-based regimens | Insufficient data to recommend |
| **NFV**-based regimens | Variable PK<br>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 **RTV** or use of **RTV** as the sole PI | GI intolerance<br>Metabolic toxicity |
| Regimens containing 3 NRTIs and 1 NNRTI | Added cost and complexity outweighs any benefit |
| **SQV**-based regimens | Limited dosing and outcome data |
| **TDF**-containing regimens in children aged <2 years | Potential bone toxicity<br>Appropriate dose has yet to be determined |
| **TPV**-based regimens | Increased dose of RTV for boosting<br>Reported cases of intracranial hemorrhage |

**Key to Abbreviations:** ABC = abacavir; ARV = antiretroviral; ART = antiretroviral therapy; ATV = atazanavir; d4T = stavudine; ddI = didanosine; DRV = darunavir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; 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 = pharmacokinetic; RTV = ritonavir; SQV = saquinavir; T20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

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

| ART Regimens Never Recommended for Children | | |
|---|---|---|
| **Regimen** | **Rationale** | **Exceptions** |
| **1 ARV Drug Alone (Monotherapy)** | • Rapid development of resistance<br>• Inferior antiviral activity compared with combination including ≥3 ARV drugs<br>• Monotherapy "holding" regimens associated with more rapid CD4 decline compared to non-suppressive ART | • Infants exposed to HIV (with negative viral testing) during 4- to 6-week period of prophylaxis to prevent perinatal transmission of HIV |
| **2 NRTIs Alone** | • Rapid development of resistance<br>• Inferior antiviral activity compared with combination including ≥3 ARV drugs | • Not recommended for initial therapy<br>• For patients currently on 2 NRTIs alone who achieve virologic goals, some clinicians may opt to continue this treatment. |
| **TDF plus ABC plus (3TC or FTC) as a Triple-NRTI Regimen** | • High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults | • No exceptions |
| **TDF plus ddI plus (3TC or FTC) as a Triple-NRTI Regimen** | • High rate of early viral failure when this triple-NRTI regimen was used as initial therapy in treatment-naive adults | • No exceptions |
| **ARV Components Never Recommended as Part of an ARV Regimen for Children** | | |
| **Regimen** | **Rationale** | **Exceptions** |
| **ATV plus IDV** | • Potential additive hyperbilirubinemia | • No exceptions |
| **Dual-NNRTI Combinations** | • Enhanced toxicity | • No exceptions |
| **Dual-NRTI Combinations:**<br>**• 3TC plus FTC** | • Similar resistance profile and no additive benefit | • No exceptions |
| **• d4T plus ZDV** | • Antagonistic effect on HIV | • No exceptions |
| **NVP as Initial Therapy in Adolescent Girls with CD4 Count >250 cells/mm³ or Adolescent Boys with CD4 Count >400 cells/mm³** | • Increased incidence of symptomatic (including serious and potentially fatal) hepatic events in these patient groups | • Only if benefit clearly outweighs risk |
| **Unboosted SQV, DRV, or TPV** | • Poor oral bioavailability<br>• Inferior virologic activity compared with other PIs | • No exceptions |

**Key to Abbreviations:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV = atazanavir; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; d4T = stavudine; ddI = didanosine; DRV = darunavir; EFV = efavirenz; 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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# Specific Issues in Antiretroviral Therapy for Neonates (Last updated April 27, 2017; last reviewed April 27, 2017)

Existing pharmacokinetic (PK) and safety data are insufficient for the recommendation of a complete antiretroviral therapy (ART) regimen to treat preterm infants and term infants younger than 15 days (until 42 weeks postmenstrual age).

Until recently, neonatal antiretroviral (ARV) regimens were designed for prophylaxis of perinatal HIV transmission and to be as simple as possible for practical use in resource-constrained countries. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV nucleic acid testing (NAT) results meant that neonatal infections were generally not diagnosed in the first weeks of life. However, HIV NAT test results now often are available within a few days and infants with HIV infection are being diagnosed as early as the first days of life. The case of prolonged remission of HIV infection in an infant from Mississippi has led to discussions about strategies to achieve prolonged virologic suppression of *in utero* HIV infection with early intensive ART and subsequent treatment interruption.[1-3] Use of such strategies must be tempered by:

- Lack of evidence that very early treatment (before age 2 weeks) will produce a prolonged remission or lead to better outcomes in infants with HIV infection;
- The very limited dosing and safety data for ARV drugs in the newborn period; and
- The potential for toxicity from ARV agents in the newborn period.

Sufficient data exist to provide dosing recommendations appropriate for the **treatment** of HIV infection in neonates using the following medications:

- From birth in term and preterm infants: zidovudine
- From birth in term neonates: lamivudine, emtricitabine, and stavudine
- From age 2 weeks in term neonates: didanosine, nevirapine, and lopinavir/ritonavir

Studies of neonatal PK and safety are ongoing for nevirapine and raltegravir in term infants and for zidovudine, lamivudine and nevirapine in low birth weight infants. For all other ARV drugs, PK and safety data are insufficient to allow recommendations for safe doses appropriate for use in neonates with HIV infection.

Data are insufficient on which to base a firm recommendation for treatment doses of nevirapine in newborn infants. Nevirapine PK data in neonates come from studies designed to identify doses appropriate for **prophylaxis, not treatment**, of HIV infection. The target plasma trough concentration in nevirapine perinatal prophylaxis studies was 0.1 microgram/mL, which would be inadequate for sustained therapeutic effect in an individual with HIV infection.[4,5] The weight band nevirapine dosing regimen used in these prophylaxis studies should be used in infants who require nevirapine for prophylaxis against HIV transmission, rather than treatment for established HIV infection (see Recommended Neonatal Dosing table in the Infant Antiretroviral Prophylaxis section of the Perinatal Guidelines). No neonatal PK data exist for regimens designed to achieve the suggested therapeutic plasma target trough concentration of 3.0 microgram/mL. A population analysis of nevirapine PK data collected during the first year of life combining both prevention studies in the first months of life and treatment studies in older infants demonstrated that nevirapine clearance is low immediately after birth and increases dramatically over the first months of life.[6] Simulations derived from this model suggest that 6 mg/kg of nevirapine administered twice daily to full-term infants (>37 weeks' gestation) in the first 4 weeks of life will maintain trough concentrations above 3.0 microgram/mL.[7] This dosing regimen is being studied in 3 newborn early treatment studies: the international multisite P1115 trial (NCT02140255), BHP-074 in Botswana (NCT02369406), and the Leopard Study in South Africa (NCT02431975). Studies of nevirapine PK in premature infants are very limited. A recent study of nevirapine trough concentrations in premature infants receiving daily nevirapine for prophylaxis against HIV transmission demonstrates that nevirapine clearance is further decreased in infants born prematurely.[8] Incorporating these data into the simulations suggests that dosing infants born between 34 and 37 weeks' gestation with 4 mg/kg of nevirapine twice daily for the first week, followed by 6 mg/kg twice daily for the next 3 weeks, should maintain trough concentrations above 3.0 micrograms/mL while avoiding excessive plasma concentrations. This dosing regimen for infants born at 34 to 37 weeks' gestation will also be evaluated in P1115. Nevirapine safety and PK are being studied in smaller and more premature infants in the P1106 protocol (NCT02383849). Careful clinical assessment of the infant, evaluation of hepatic and renal function, and review of concomitant medications should be performed when using nevirapine in premature infants.

The experience with lopinavir/ritonavir in neonates highlights the risk of using ARV drugs in neonates without neonatal PK and safety data. Life-threatening cardiovascular, renal, and central nervous system (CNS) toxicity have been reported in 10 infants (8 preterm, 2 term) receiving lopinavir/ritonavir oral solution during the first weeks of life. These toxicities included bradycardia, complete atrioventricular block, heart failure, renal failure, respiratory failure, metabolic acidosis, hypotonia, CNS depression, and one infant died of cardiogenic shock.[9] Lopinavir/ritonavir oral solution contains ethanol (42.4% w/v) and propylene glycol (15.3% w/v), and the contributions of lopinavir, ritonavir, ethanol, and propylene glycol exposure to the observed toxicities are not clear. While a small study of trough lopinavir plasma concentrations in premature infants and a larger-population PK study in infants including neonates provide some preliminary PK data, they are insufficient to currently allow a recommendation for safe and effective lopinavir/ritonavir treatment dosing immediately following birth.[10,11] In a large trial, lopinavir/ritonavir was as effective and well tolerated as lamivudine when used for prophylaxis against HIV transmission when administered from 1 week of age through cessation of breast feeding.[12] The Food and Drug Administration recommends against the use of lopinavir/ritonavir oral solution in premature infants until 14 days after their due date, or in full-term infants younger than 42 weeks postmenstrual age.[9]

While there is considerable interest in the use of integrase inhibitors in neonates, data are lacking to formulate a safe dosing recommendation in neonates. Neonatal washout elimination of raltegravir that crossed the placenta after maternal administration is highly variable, with a half-life ranging from 9.3 to 184 hours over the first days of life.[13] Investigation of a daily-dosing raltegravir regimen in neonates is underway in the P1110 protocol (NCT01780831). As raltegravir competes with bilirubin for protein binding and for elimination through glucuronidation, increased plasma raltegravir concentrations may lead to increased plasma concentrations of free unconjugated bilirubin, posing the risk of bilirubin encephalopathy and kernicterus, particularly in preterm infants who have decreased bilirubin elimination, decreased albumin binding capacity and an immature blood-brain barrier.[14] Use of the recently approved oral granule raltegravir formulation in neonates should be avoided until adequate neonatal PK and safety data are available (see Recommended Neonatal Dosing table in the Infant Antiretroviral Prophylaxis section of the Perinatal Guidelines).

Current recommendations for ARV prophylaxis for prevention of perinatal HIV transmission in high-risk infants in the United States (e.g., limited or no prenatal maternal ART, high maternal viral load) are for use of zidovudine and nevirapine dosed according to the NICHD-HPTN 040 regimen.[15,16] The nevirapine regimen used in NICHD-HPTN 040 was designed to maintain nevirapine concentrations above 0.1 microgram/mL, the drug concentration target used in studies of prevention of HIV transmission, not the 3.0 microgram/mL target used in treatment of individuals with HIV infection.[17] In this study, both 2- and 3-drug combination regimens were superior to zidovudine prophylaxis alone to prevent intrapartum transmission; however, there was no incremental benefit of the 3-drug regimen (lamivudine and nelfinavir for 2 weeks plus zidovudine for 6 weeks) compared to the 2-drug regimen (3 doses of nevirapine in the first week of life plus 6 weeks of zidovudine) in prevention of perinatal transmission. The 3-drug regimen had significantly more hematologic toxicity and the powder nelfinavir formulation is no longer commercially available. A retrospective comparison of safety outcomes in Canadian high-risk newborns exposed to HIV treated with either zidovudine alone or 3-drug combination regimens (zidovudine, lamivudine and either nevirapine, nelfinavir, or lopinavir/ritonavir) also found transient decreased mean hemoglobin over the first 6 months of life in infants treated with 3-drug ART regimens.[18]

Despite these data, combination treatment of infants at high risk of HIV infection for presumptive HIV infection has been increasing in recent years. EPPICC has pooled data from 5,285 mother-infant pairs considered at high risk of perinatal transmission (no antepartum maternal treatment or detectable maternal viremia despite treatment) included in 8 European cohorts and evaluated the use of combination prophylaxis. Among the 1,105 infants receiving combination prophylaxis, 13.5% received zidovudine plus lamivudine, 22.7% received zidovudine plus single-dose nevirapine, 55.8% received zidovudine plus single-dose nevirapine plus lamivudine, and 4.4% received a regimen including a protease inhibitor. In these observational cohorts, there was no difference in infant infection rates between one drug and combination prophylactic regimens.[19] As discussed above, the data necessary for safe and appropriate neonatal dosing of all components of a 3-drug ARV regimen for treatment of HIV infection are not currently available.

The risks associated with use of a 3-drug ART regimen in neonates as well as the potential benefits, including the possibility of prolonged remission in neonates with HIV infection, require further study before a general recommendation can be made. The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends that neonatal care providers who are considering a 3-drug ART regimen in term infants younger than 2 weeks or premature infants contact a pediatric HIV expert for guidance and individual case assessment of the risk/benefit ratio of treatment and for the latest information on neonatal drug doses. Providers can contact a local pediatric HIV expert or the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on perinatal HIV care.

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# Specific Issues in Antiretroviral Therapy for Adolescents Living with HIV Infection (Last updated April 27, 2017; last reviewed April 27, 2017)

| **Panel's Recommendations** |
|---|
| • Antiretroviral therapy (ART) selection should take into account the adolescent's individual needs and preferences **(AIII)**.<br>• Reproductive health including preconception care and contraceptive methods, and safe sex techniques to prevent HIV transmission should be discussed regularly **(AI)**.<br>• All adolescents, including those who are considering pregnancy, should be receiving maximally suppressive ART **(AII)**.<br>• Providers should be aware of potential interactions between ART and hormonal contraceptives that could lower contraceptive efficacy **(AII*)**.<br>• 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*<br><br>***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*<br><br>*† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents* |

## Background

Most individuals in the United States who acquired HIV infection through perinatal transmission are now adolescents or young adults. Of the indiviuals who acquired HIV infection through perinatal transmission in the United States—1,999 are aged less than 13 years with an estimated 9,131 adults and adolescents (aged >13 years) as of December 2013.[1] Most have had a long clinical course with an extensive history of treatment with antiretroviral therapy (ART).[2,3] Many older youth initially received non-suppressive mono- or dual therapy prior to the availability of combination regimens. Challenges in the treatment of adolescents with perinatally acquired HIV infection include extensive drug resistance, complex regimens, and the long-term consequences of HIV and ART exposure.

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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (Adult and Adolescent Guidelines) should be used for treatment recommendations.[4]

## 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 atazanavir) that have a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors.[5]

In addition, many antiretroviral (ARV) drugs (e.g., abacavir, emtricitabine, lamivudine, tenofovir disoproxil fumarate [TDF], and some protease inhibitors [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. This is based upon reported PK data indicating more rapid drug clearance in children.

The choice of ART, specifically for TDF is based on sexual maturity rating (SMR, formerly Tanner staging) and not on age, related to concerns for associated toxicity.

## Timing and Selection of ART

All individuals, including adolescents living with HIV, should initiate ART promptly. Optimal dosing recommendations for initial therapy that are pertinent to adolescents whose SMR is between I and III are available in Appendix A: Pediatric Antiretroviral Drug Information and What to Start. Recommendations for initial therapy for adolescents and young adults whose SMR is between IV and V are available in the What to Start section of the Adult and Adolescent Guidelines. These recommendations also 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, with pre-treatment CD4 T lymphocyte (CD4) counts >500 cells/mm$^3$, than when initiated at a lower CD4 cell count threshold.[6,7]

## 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.[8-10] For a further discussion of interventions to promote adherence in adolescents, see the HIV-Infected Adolescents section of the Adult and Adolescent Guidelines and a review by Agwu and Fairlie.[11]

A particular challenge is presented by youth who, despite interventions, remain unable to adhere to therapy. In these cases, alternative considerations to initiating or changing ARV therapy can include: 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, and the avoidance of any regimens with low genetic resistance barriers. Such decisions should be individualized and the patient's clinical and laboratory status monitored carefully.

## Sexually Transmitted Diseases in Adolescents

Sexually transmitted diseases (STDs), including human papilloma virus (HPV), should be addressed in all adolescents. In young men who have sex with men, screening for STDs often requires sampling from several body sites, including the oropharynx, rectum, and urethra, since multiple sites of infection are common.[12] For a more detailed discussion of STDs, see the most recent Centers for Disease Control and Prevention guidelines,[13] the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (Adult and Adolescent OI Guidelines), and Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children (Pediatric OI Guidelines) on HPV among youth living with HIV.[14,15] All female adolescents living with HIV who are sexually active should receive gynecologic care and all adolescents should be immunized with HPV vaccination.

## Adolescent Contraception, Pregnancy, and Antiretroviral Therapy

Adolescents living with HIV may initiate sexual activity before or after puberty. Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods for reducing risks, should be provided to all youth. Reproductive health options including pregnancy planning, preconception care, contraception methods, and safer sex techniques (including 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).[16] For additional information readers are referred to The Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States (Perinatal Guidelines) section entitled Reproductive Options for HIV-Concordant and Serodiscordant Couples.[17]

The possibility of planned and unplanned pregnancy should also 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 Perinatal Guidelines).[17] Readers should consult the Perinatal Guidelines for guidance in selection of ARV drugs during pregnancy.

### *Contraceptive-Antiretroviral Drug Interactions*

Women living with HIV can use all available contraceptive methods, including the transdermal patch and vaginal ring.

Several PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) drugs alter metabolism of oral contraceptives, which 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 http://www.hiv-druginteractions.org).[18-20] Integrase inhibitors (specifically raltegravir) appear to have no interaction with estrogen-based contraceptives.[21] 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.[22]

### *Pregnant Adolescents Living with HIV*

Adolescents who want to become pregnant should be referred for preconception counseling and care, including discussion of special considerations for use of ART during pregnancy (see Perinatal Guidelines).[17] 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 non-pregnant women. Details regarding choice of ART regimen in pregnant women living with HIV, including adolescents, are provided in the Perinatal Guidelines.[17] Pregnancies are currently being reported as girls with perinatally acquired HIV infection enter adolescence and young adulthood.[23,24] Some studies suggest higher rates of adverse pregnancy outcome, such as small-for-gestational-age infants, among pregnant women with perinatal compared to horizontal infection, and unplanned pregnancy appears frequent.[24-26] However, the rate of perinatal transmission among pregnant women with perinatally acquired HIV infection who are receiving ART appears similar to that among women on ART who acquired HIV by horizontal transmission.[27-31]

## Transition of Adolescents into Adult HIV Care Settings

Facilitating a seamless transition of adolescents living with HIV from their pediatric/adolescent medical home to adult care is important but challenging. 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, the transition process should be initiated early in the second decade of life. 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.”[32] 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, more 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 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 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 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, after-school appointments). Additional factors that should be considered during transition include social determinants such as developmental status, behavioral/mental health issues, housing, family support, employment, 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.[33-36]

Currently there is no definitive model of transition to adult HIV care and only limited reports about outcomes following transition. In some settings, youth followed in 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.[10] A report from the United Kingdom suggests an increased risk of mortality after transition.[35] In a report from a Baltimore clinic on 50 youth (31 non-perinatally and 19 perinatally-acquired HIV), although 86% were successfully transitioned and linked to adult care, only 50% were retained in care 12 months after transition.[37] Another study that examined the continuum of care for youth with perinatally acquired HIV, using surveillance data in New York city, reported worsening rates of retention and lower rates of viral suppression with increasing age. Rates of continuous engagement in care and viral suppression were 89% and 67%, respectively, for individuals aged 13 to 19 years decreasing to 76% and 58% for those aged 20 to 29 years, underscoring the need to critically examine transition and determine best mechanisms to optimize the long-term outcomes for youth with perinatal HIV infection.[3]

Some general guidelines, mostly based on anecdotal evidence and consensus expert opinion, are available about transitional plans and who might benefit most from them.[38-45] 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 interruptions to ART:

- 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 and adult clinics;
- Identifying adult care providers who have expertise in providing care to adolescents and young adults;
- Addressing patient/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 the appropriate use of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and the importance of self-efficacy in managing medications, insurance, and entitlements;
- 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);
- Implementing ongoing evaluation 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 and before the actual transition process.

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# Adherence to Antiretroviral Therapy in Children and Adolescents Living with HIV (Last updated April 27, 2017; last reviewed April 27, 2017)

| Panel's Recommendations |
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| • Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again before changing regimens **(AIII)**.<br>• Adherence to therapy must be assessed and promoted at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**.<br>• At least one method of measuring adherence to ART should be used in addition to monitoring viral load **(AIII)**.<br>• 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*<br>***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*<br>*† 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.[1] Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, as well as sub-therapeutic or partial dosing.[2,3] Poor adherence will result in sub-therapeutic plasma antiretroviral (ARV) drug concentrations, facilitating development of drug resistance to 1 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.[4] In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens in patients who develop multidrug-resistant HIV and for increasing the risk of secondary transmission.

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 and behavioral 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.[5] Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.[6] 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.[7] The limited availability of once-daily and single-tablet regimens and palatable formulations for infants and young children is especially problematic.[8] 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.[9,10] Some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.[11] 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).[12]

## 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 past experience 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), how they can be managed and 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.[13-15] 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). In addition, it can be used as positive reinforcement to encourage continued adherence.[16] Use of at least one other method in addition to monitoring viral load to assess adherence is recommended.[15,17] Table 11 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 particular 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 optimization of the drug regimen and the development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (e.g., associating medication administration with daily activities such as brushing teeth), and 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.[11,18,19] 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.[18,20-24] Table 12 summarizes some of the strategies that can be used to support and improve adherence to ARV medications. The Centers for Disease Control and Prevention offers a web-based toolkit (consisting of 4 evidence-based HIV medication adherence strategies) to HIV care providers (located at http://www.effectiveinterventions.org/en/HighImpactPrevention/BiomedicalInterventions/MedicationAdherence.aspx).[25]

### *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.[26] Efforts should be made to reduce the pill burden 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.[8,27]

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).[28] 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.[29] Finally, if drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs or change the particular drug (or, if necessary, drug regimen) when feasible.

### *Patient/Family-Related Strategies*

The primary approach taken by the clinical team 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 reasons for making adherence a priority, 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.

A number of 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.[30] Availability of mental health services and the treatment of mental health disorders (such as depression) may facilitate adherence to complex ARV drug regimens.[31] A gastrostomy tube should be considered for nonadherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications.[32] If adequate resources are available, home-nursing interventions or DOT may also be beneficial.

Other strategies to support adherence include 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. Randomized clinical trials in adults have demonstrated that text messaging is associated with improved adherence[33-37] and a recent study in poorly adherent HIV-positive adolescents and young adults demonstrated that 2-way personalized daily text messaging improved self-reported adherence.[38] It should be noted, however, that the evidence base for effective adherence interventions in adolescents and young adults taking daily ART is limited.[39-41]

### *Health Care Provider-Related Strategies*

To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with patients/caregivers, and identify mutually acceptable goals for care. Providers have the ability to 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.[42] Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking 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.[43] 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 11. Evidence-Based Approaches for Monitoring Medication Adherence

| Routine Assessment of Medication Adherence in Clinical Care[a] | Description |
|---|---|
| Monitor viral load. | Viral load monitoring should be done more frequently after initiating or changing medications.[a] |
| Assess quantitative self-report of missed doses. | Ask 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, home visits, or referral to community health nursing. |
| **Targeted Approaches to Monitor Adherence in Special Circumstances** | **Description** |
| Implement directly observed therapy. | Include brief hospitalization if indicated. |
| Measure plasma drug concentration. | Can be considered for particular drugs.[b] |
| **Approaches to Monitor Medication Adherence in Research Settings** | **Description** |
| Measure drug concentrations in hair. | Good measure of adherence over time.[c] |
| Use electronic monitoring devices. | Medication Event Monitoring System [MEMS] caps, Wisepill |
| Use mobile phone-based technologies. | Interactive voice response, SMS text messaging |

[a] 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.

[b] See Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection regarding indications for therapeutic drug monitoring.

[c] Source: Olds PK, Kiwanuka JP, Nansera D, et al. Assessment of HIV antiretroviral therapy adherence by measuring drug concentrations in hair among children in rural Uganda. AIDS Care. 2015;27(3):327-332. Available at https://www.ncbi.nlm.nih.gov/pubmed/25483955.[44]

## Table 12. 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 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. |
| • Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen. |

**Table 12. Strategies to Improve Adherence to Antiretroviral Medications**

| Medication Strategies |
|---|
| • Choose the simplest regimen possible, reducing dosing frequency 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, 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 selected circumstances, during a brief inpatient hospitalization. |
| • Consider gastrostomy tube use in selected circumstances. |
| • Information on other interventions to consider can be found at http://www.cdc.gov/hiv/prevention/research/compendium/ma/complete.html. |

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

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# Management of Medication Toxicity or Intolerance (Last updated April 27, 2017; last reviewed April 27, 2017)

| 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*)**.<br>• 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*)**.<br>• The toxicity and the medication presumed responsible should be documented in the medical record and the caregiver and patient advised of the drug-related toxicity **(AIII)**.<br>• In general, dose reduction is not a recommended option for management of ARV toxicity **(AII*)**. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***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*<br>*† 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 Adult ARV Guidelines).[1]

Fortunately, currently recommended ARV regimens are associated with fewer serious and intolerable AEs than regimens used in the past. Generally, less than 10% of ART-naive patients enrolled in randomized trials have treatment-limiting AEs.[2-12] Some longer-term complications of ART (e.g., bone or renal toxicity, dyslipidemia, or 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.[13-15] 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).[14-17] 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 and Role of Therapeutic Drug Monitoring in Management of

Pediatric HIV Infection).

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 and 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 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 with atazanavir, renal tubulopathy with 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 severity of the toxicity, the relative need for further viral suppression, and the available ARV options. Common, self-limited AEs should be anticipated, and reassurance provided 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. Central nervous system 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. They 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.[18-20] In addition, mild rash can be ameliorated with drugs such as antihistamines. For some moderate toxicities, using a drug in the same class as the one causing toxicity but with a different toxicity profile may be sufficient and discontinuation of all therapy may not be required.

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.[21,22] Many experts will stagger a planned interruption of a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, stopping the NNRTI first and the dual nucleoside analogue reverse transcriptase backbone 7 to 14 days later because of the long half-life of NNRTI drugs. For patients who have a severe or life-threatening toxicity (e.g., hypersensitivity reaction—see Hypersensitivity Reaction, Table 13l), however, all components of the drug regimen should be stopped simultaneously, regardless of drug half-life. Once the offending drug or alternative cause for the AE has been determined, planning can begin for resumption of therapy with a new ARV regimen that does not contain the offending drug or 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.[23-27] Clinicians should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, changing a single drug in a multidrug regimen is permissible 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 a recommended strategy for the management of toxicity due to concern for decreased virologic efficacy with inadequate ARV drug levels. 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[28,29] (see Role of Therapeutic Drug Monitoring). An expert in the management of pediatric HIV infection 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.
- Changing from one drug to another drug to which a patient's virus is susceptible (such as changing to abacavir for zidovudine-related anemia or to a PI or integrase strand transfer inhibitor (INSTI) for efavirenz-related CNS symptoms).
- Changing drug classes (e.g., from a PI to an INSTI or a NNRTI or vice versa) if a patient's virus is susceptible to a drug in that class.
- Using dose reduction as guided by TDM in consultation with an expert in pediatric HIV infection.

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## Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 3)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Global CNS Depression** | LPV/r oral solution (contains both ethanol and propylene glycol as excipients) | Onset:<br>• 1–6 days after starting LPV/r<br>Presentation<br>*Neonates/Premature Infants:*<br>• Global CNS depression (e.g., abnormal EEG, altered state of consciousness, somnolence) | Unknown, rare case reports | Prematurity<br>Low birth weight<br>Age <14 days (whether premature or term) | Avoid use of LPV/r until a postmenstrual age of 42 weeks and a postnatal age ≥14 days. | Discontinue LPV/r; symptoms should resolve in 1–5 days.<br>If needed, reintroduction of LPV/r can be considered once outside the vulnerable period (i.e., postmenstrual age of 42 weeks and a postnatal age ≥14 days). |
| **Neuropsychiatric Symptoms and Other CNS Manifestations** | EFV | Onset:<br>• 1–2 days after initiating treatment for many symptoms<br>• Many symptoms subside or diminish by 2–4 weeks, but may persist in a significant proportion of patients. In one report, 37% experienced persistent symptoms at 12 months and in another, half of discontinuations occurred after 12 months.<br>Presentation (May Include One or More of the Following)<br>*Neuropsychiatric Symptoms:*<br>• Abnormal dreams<br>• Psychosis<br>• Suicidal ideation or attempted/ completed suicide<br>*Other CNS Manifestations:*<br>• Dizziness<br>• Somnolence<br>• Insomnia or poor sleep quality<br>• Impaired concentration<br>• Seizures (including absence seizures) | Variable, depending on age, symptom, assessment method<br>Children:<br>• 24% for any EFV-related CNS manifestations in 1 case series with 18% requiring drug discontinuation<br>• 9% incidence of new-onset seizures reported in 1 study in children aged <36 months. In 2 of the children the seizures had alternative causes.<br>• Cases of cerebellar dysfunction have been reported in children in association with very high EFV plasma levels.<br>Adults:<br>• 30% incidence for any CNS manifestations of any severity.<br>• 6% incidence for EFV-related severe CNS manifestations including suicidality. However, evidence is conflicting about whether EFV use increases the incidence of suicidality. | Insomnia associated with elevated EFV trough concentration ≥4 mcg/mL<br>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)<br>Prior history of psychiatric illness or use of psychoactive drugs | Administer EFV on an empty stomach, preferably at bedtime.<br>Prescreen for and avoid use in the presence of psychiatric illness including depression or suicidal thoughts or with concomitant use of psychoactive drugs.<br>TDM can be considered in the context of a child with mild or moderate toxicity possibly attributable to a particular ARV agent (see Role of Therapeutic Drug Monitoring in Management of Treatment Failure). | Obtain EFV trough concentration if symptoms excessive or persistent. If EFV trough concentration >4 mcg/mL, strongly consider drug substitution if suitable alternative exists. Alternatively, consider dose reduction with repeat TDM and dose adjustment (with expert pharmacologist input).<br>In a small study, cyproheptadine was shown to reduce short-term incidence of neuropsychiatric effects in adults receiving EFV, but data are lacking in children and no recommendation can be made for its use at this time. |

## Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 3)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Neuropsychiatric Symptoms and Other CNS Manifestations** | EFV | • Cerebellar dysfunction (tremor, dysmetria, ataxia)<br><br>**Note:** Some CNS side effects (e.g., impaired concentration, abnormal dreams, or sleep disturbances) may be more difficult to assess in children. | | | | |
| | RPV | <u>Presentation</u><br>*Neuropsychiatric Symptoms:*<br>• Depressive disorders<br>• Suicidal ideation<br>• Abnormal dreams/nightmares<br>*Other CNS Manifestations:*<br>• Headache<br>• Dizziness<br>• Insomnia<br>• Somnolence | <u>In Adults</u>:<br>• 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.<br><u>In Children</u>:<br>• Depressive disorders of all severity grades were reported in 19.4% of pediatric patients aged 12 years to 17 years. Severe depressive disorders were reported in 5.6% of patients, including a suicide attempt in 1 subject.<br>• Somnolence reported in 5/36 (14%) children. | Prior history of neuropsychiatric illness | Monitor carefully for depressive disorders and other CNS symptoms. | Consider drug substitution in case of severe symptoms. |
| | RAL | <u>Presentation</u>:<br>• Increased psychomotor activity<br>• Headaches<br>• Insomnia<br>• Depression<br>• Cerebellar dysfunction (e.g., tremor, dysarthria, ataxia) | <u>Children</u>:<br>• Increased psychomotor activity reported in one child.<br><u>Adults</u>:<br>• Headache<br>• Insomnia (<5% in adult trials)<br>• Rare case reports of cerebellar dysfunction in adults | Elevated RAL concentrations<br><br>Co-treatment with TDF or PPI or inhibitors of UGT1A1<br><br>Prior history of insomnia or depression | Prescreen for psychiatric symptoms.<br><br>Monitor carefully for CNS symptoms.<br><br>Use with caution in the presence of drugs that increase RAL concentration. | Consider drug substitution (RAL or co-administered drug) in case of severe insomnia or other neuropsychiatric symptoms. |

## Table 13a. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Central Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017) (page 3 of 3)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| | DTG | Onset:<br>• 7–30 days after initiating drug<br>Presentation<br>*Neuropsychiatric Symptoms:*<br>• Depression or exacerbation of preexisting depression<br>• Anxiety<br>• Suicidal ideation attempt, behavior, or completion<br>*Other CNS Manifestations (Generally Mild):*<br>• Insomnia<br>• Dizziness<br>• Headache | Adults:<br>• Exact frequency of neuropsychiatric symptoms is unknown; case reports of 4 adult patients. Headache, insomnia, and dizziness are common, reported in up to 10% of patients. Less than 1% of patients experienced more severe symptoms. | Pre-existing depression or other psychiatric illness | Use with caution in the presence of psychiatric illness, especially depression. | For severe neuropsychiatric symptoms, consider discontinuation of DTG if suitable alternative exists.<br>Discontinuation resulted in resolution of neuropsychiatric symptom in 3 out of 4 patients (in the fourth patient, symptoms resolved slowly despite DTG continuation).<br>For mild symptoms, continue DTG and counsel patient that symptoms will likely resolve with time. |
| **Intracranial Hemorrhage** | TPV | *Onset*:<br>• 7–513 days after starting TPV | Children:<br>• No cases of ICH reported in children.<br>Adults:<br>• 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. | Unknown; prior history of bleeding disorder or risk factors for bleeding present in most patients in case series reported. | 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:** ARV = antiretroviral; ATV = atazanavir; CNS = central nervous system; CYP = cytochrome P; DTG = dolutegravir; EEG = electroencephalogram; EFV = efavirenz; ICH = intracranial hemorrhage; LPV/r = ritonavir-boosted lopinavir; 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 13b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia

**(Last updated April 27, 2017; last reviewed April 27, 2017)** (page 1 of 2)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Dyslipidemia** | PIs:<br>• All PIs, especially RTV-boosted PIs; lower incidence reported with DRV/r and ATV with or without RTV.<br><br>NRTIs:<br>• Especially d4T<br><br>NNRTIs:<br>• EFV > NVP, RPV, and ETR | Onset:<br>• As early as 2 weeks to months after beginning therapy<br><br>Presentation<br>*PIs:*<br>• ↑LDL-C, TC, and TG<br><br>*NNRTIs:*<br>• ↑LDL-C, TC, and HDL-C<br><br>*NRTIs:*<br>• ↑LDL-C, TC, and TG | Reported frequency varies with specific ARV regimen, duration of ART and specific laboratory parameters used to diagnose lipid abnormalities.<br><br>10% to 20% in young children receiving LPV/RTV.<br><br>40% to 75% of older children and adolescents with prolonged ART history will have lipid abnormalities.<br><br>Higher abnormal fasting serum lipids in EVG/COBI/FTC/TAF vs. EVG/COBI/FTC/TDF regimen in studies of treatment- naive adults<br><br>Increase in serum lipids from baseline also noted in adolescents receiving EVG/COBI/FTC/TAF | Advanced-stage HIV disease<br><br>High-fat, high-cholesterol diet<br><br>Lack of exercise<br><br>Obesity<br><br>Hypertension<br><br>Smoking<br><br>Family history of dyslipidemia or premature CVD<br><br>Metabolic syndrome<br><br>Fat maldistribution | Prevention:<br>• Low-fat diet<br>• Exercise<br>• Smoking-prevention counseling<br>• Avoid d4T<br><br>Monitoring[a]<br>*Adolescents and Adults:*<br>• Monitor 12-hour FLP, which includes TC, HDL-C, non-HDL-C, LDL-C, and TG, every 6–12 months. Obtain FLPs twice (>2 weeks but ≤3 months apart, average results) before initiating or changing lipid-lowering therapy.<br><br>*Children (Aged ≥2 Years) without Lipid Abnormalities or Additional Risk Factors:*<br>• Obtain non-fasting 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.<br><br>*Children with Lipid Abnormalities and/or Additional Risk Factors:*<br>• Obtain 12-hour FLP before initiating or changing therapy and every 6 months thereafter (more often if indicated). | 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.[b]<br><br>Counsel on lifestyle modification, dietary interventions (e.g., a diet low in saturated fat, cholesterol, and refined sugars particularly in case of ↑TG, elimination of transfat, physical activity, smoking cessation) for an adequate trial period (3–6 months). Consider consultation with dietician.<br><br>ART regimen changes can be considered. Discontinue d4T or substitute a PI-sparing regimen or PI-based regimen with a more favorable lipid profile.<br><br>Consider lipid-lowering therapy in consultation with a lipid specialist if ≥6-month trial of lifestyle modification fails.<br><br>Some experts suggest treatment in 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.[b]<br><br>The minimal goal of therapy should be to achieve and maintain a LDL-C value below 130 mg/dL, while maintaining viral control. |

## Table 13b. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Dyslipidemia (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 2)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Dyslipidemia**, continued | | | | | *Children Receiving Lipid-Lowering Therapy with Statins or Fibrates:*<br>• Obtain 12-hour FLP, LFTs, and CK at 4 and 8 weeks, and 3 months after starting lipid therapy.<br>• 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).<br>• Repeat FLPs 4 weeks after increasing doses of antihyperlipidemic agents. | Statins such as pravastatin, atorvastatin, or rosuvastatin[c] can be considered.[d] 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.[c] Statins may also increase the risk of insulin resistance and diabetes mellitus. Risks must be weighed against potential benefits. Cholesterol absorption inhibitors (e.g., ezetimibe) can be considered as alternative.<br><br>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.<br><br>The long-term risks of lipid abnormalities in children receiving ART are unclear. However, persistent dyslipidemia in children may lead to premature CVD. |

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

[b] Refer to NHLBI guidelines at http://www.nhlbi.nih.gov/guidelines/cvd_ped/summary.htm#chap9.

[c] 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.

[d] Statins (HMG-CoA reductase inhibitors) are contraindicated in pregnancy (potentially teratogenic) and should not be used in patients who may become pregnant. Multiple drug interactions exist between ARV drugs and statins (exception 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

**Key to Acronyms:** ALT = alanine aminotransferase; ART = antiretroviral therapy; ARV = antiretroviral; AST = aspartate aminotransferase; ATV = atazanavir; CK = creatine kinase; CVD = cardiovascular disease; CYP3A4 = cytochrome P450 3A4; d4T = stavudine; DRV = darunavir; DRV/r = ritonavir-boosted darunavir; EFV = efavirenz; ETR = etravirine; FLP = fasting lipid profile; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; LPV = lopinavir; 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; TC = total cholesterol; TG = triglyceride

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## Table 13c. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Gastrointestinal Effects (Last updated April 27, 2017; last reviewed April 27, 2017)

| Adverse Effects. | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Nausea/ Vomiting** | Principally ZDV and PIs, but can occur with all ARVs and COBI | Onset:<br>• Early<br>Presentation:<br>• Nausea, emesis—may be associated with anorexia and/or abdominal pain. | Varies with ARV agent; 10% to 30% in some series | Unknown | Instruct patient to take PIs with food.<br>Monitor for weight loss, ARV adherence. | Reassurance—generally improves over time (usually 6–8 weeks)<br>Supportive care.<br>Antiemetics may be useful in extreme or persistent cases. |
| **Diarrhea** | PIs (particularly NFV, LPV/r, FPV/r), buffered ddI, INSTIs (mild) | Onset:<br>• Early<br>Presentation:<br>• Generally soft, more frequent stools | Varies with ARV agent; 10% to 30% in some series | Unknown | Monitor for weight loss, dehydration. | Exclude infectious causes of diarrhea if prolonged or severe.<br>Reassurance—generally improves over time (usually 6–8 weeks)<br>Although treatment data in children are lacking, potentially useful modalities include:<br>• Dietary modification<br>• Calcium carbonate (should not be used with DTG)<br>• Bulk-forming agents (psyllium)<br>• Antimotility agents (loperamide)<br>• Crofelemer is FDA-approved for treatment of ART-associated diarrhea in adults, but **not in children**. |
| **Pancreatitis** | ddI, d4T (especially concurrently), boosted PIs<br>Reported, albeit rarely, with most ARVs. | Onset:<br>• Any time, usually after months of therapy<br>Presentation:<br>• Emesis, abdominal pain, elevated amylase and lipase (asymptomatic hyperamylasemia or elevated lipase do not in and of themselves indicate pancreatitis). | <2% in recent series | Use of concomitant medications associated with pancreatitis (e.g., TMP-SMX, pentamidine, ribavirin)<br>Hypertriglyceridemia<br>Advanced disease<br>Previous episode of pancreatitis<br>Alcohol use | Avoid use of ddI in patients with a history of pancreatitis. | Discontinue offending agent—avoid reintroduction.<br>Manage symptoms of acute episode.<br>If associated with hypertriglyceridemia, consider interventions to lower TG levels. |

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DTG = dolutegravir; FDA = Food and Drug Administration; FPV/r = fosamprenavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NFV = nelfinavir; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate; TG = triglyceride; TMP-SMX = trimethoprim sulfamethoxazole; ZDV = zidovudine

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## Table 13d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)

| Adverse Effects | Associated ARVs | Onset/ Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Anemia**[a] | ZDV | Onset:<br>• Variable, weeks to months<br>Presentation<br>*Most Commonly:*<br>• Asymptomatic or mild fatigue<br>• Pallor<br>• Tachypnea<br>*Rarely:*<br>• Congestive heart failure | Newborns Exposed to HIV:<br>• Severe anemia is uncommon, but may be seen coincident with physiologic Hgb nadir.<br>Children Living with HIV on ARVs:<br>• 2–3 times more common with ZDV-containing regimens | Newborns Exposed to HIV:<br>• Premature birth<br>• *In utero* exposure to ARVs<br>• Advanced maternal HIV<br>• Neonatal blood loss<br>• Combination ARV prophylaxis, particularly with ZDV plus 3TC<br>Children Living with HIV on ARVs:<br>• Underlying hemoglobinopathy (e.g., sickle cell disease, G6PD deficiency)<br>• Myelosuppressive drugs (e.g., TMP-SMX, rifabutin)<br>• Iron deficiency<br>• Advanced or poorly controlled HIV disease<br>• Malnutrition | Newborns Exposed to HIV:<br>• Obtain CBC at birth.<br>• 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).<br>Children Living with HIV on ARVs:<br>• Avoid ZDV in children with moderate to severe anemia when alternative agents are available.<br>• Obtain CBC as part of routine care. | Newborns Exposed to HIV:<br>• Rarely requires intervention unless Hgb is <7.0 g/dL or is associated with symptoms.<br>• Consider discontinuing ZDV if 4 weeks or more of prophylaxis has been completed (see the Perinatal Guidelines[b]).<br>Children Living with HIV on ARVs:<br>• Discontinue non-ARV, marrow-toxic drugs, if feasible.<br>• Treat coexisting iron deficiency, OIs, malignancies.<br>• For persistent severe anemia thought to be associated with ARVs, change to a non-ZDV-containing regimen |
| **Macrocytosis** | ZDV; also d4T | Onset:<br>• Within days to weeks of starting therapy<br>• MCV often >100 fL<br>Presentation:<br>• Most often asymptomatic.<br>• Sometimes associated with anemia (occurs more often with ZDV than with d4T). | >90% to 95%, all ages | None | Obtain CBC as part of routine care (see Laboratory and Clinical Monitoring section). | None required unless associated with anemia. D4T is no longer recommended and should be discontinued. |

## Table 13d. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hematologic Effects (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 2)

| Adverse Effects | Associated ARVs | Onset/ Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Neutropenia**[a] | ZDV | Onset:<br>• Variable<br>Presentation:<br>• Most commonly asymptomatic. | Newborns Exposed to HIV:<br>• Rare<br>Children Living with HIV on ARVs:<br>• 2.2% to 26.8% of children on ARVs, depending upon the ARV regimen. 2.2% for ZDV/3TC<br>• Highest rates with ZDV-containing regimens. | Newborns Exposed to HIV:<br>• *In utero* exposure to ARVs<br>• Combination ARV prophylaxis, particularly with ZDV plus 3TC<br>Children Living with HIV on ARVs:<br>• Advanced or poorly controlled HIV infection<br>• Myelosuppressive drugs (e.g., TMP-SMX, ganciclovir, hydroxyurea, rifabutin) | Children Living with HIV on ARVs:<br>• Obtain CBC as part of routine care. | Newborns Exposed to HIV:<br>• No established threshold for intervention; some experts would consider using an alternative NRTI for prophylaxis if ANC <500 cells/mm$^3$, or discontinue prophylaxis if ≥4 weeks of ZDV have been completed (see the Perinatal ARV Guidelines[b]).<br>Children Living with HIV on ARVs:<br>• Discontinue non-ARV marrow-toxic drugs, if feasible.<br>• Treat coexisting OIs and malignancies.<br>• For persistent severe neutropenia thought to be associated with ARVs, change to a non-ZDV-containing regimen. |

[a] HIV infection itself, OIs, and medications used to prevent OIs, such as TMP-SMX, may all contribute to anemia, neutropenia, and thrombocytopenia.

[b] *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*

**Key to Acronyms:** 3TC = lamivudine; ANC = absolute neutrophil count; ARV = antiretroviral; CBC = complete blood count; d4t = stavudine; 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 13e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

**(Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)**

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Hepatitis** | • Most ARVs have been associated with hepatitis, but there is a strong association with NVP, EFV, and TPV<br>• NVP, EFV, ABC, RAL, and MVC have all been associated with hepatitis in context of hypersensitivity reactions<br>• NRTIs (especially ZDV, ddI, and d4T) have been associated with lactic acidosis and hepatic steatosis | Onset:<br>• An acute toxic hepatitis most commonly occurs within the first few months of therapy, but can occur later.<br>• Steatosis presents after months to years of therapy.<br>• Patients with HBV coinfection may develop flare of hepatitis with the initiation of, withdrawal of, or development of resistance to 3TC, FTC, or TDF (especially if receiving only 1 anti-HBV agent).<br>• Hepatitis may represent IRIS early in therapy, especially in patients with HBV- and HCV-coinfection.<br>Presentation:<br>• Asymptomatic elevation of AST and ALT<br>• Symptomatic hepatitis with nausea, fatigue, and jaundice<br>• Hepatitis may present in context of hypersensitivity reaction with rash, lactic acidosis, and hepatic steatosis. | Uncommon | HBV or HCV coinfection<br>Other underlying liver disease<br>Use of other hepatotoxic medications (e.g., St. John's wort [*Hypericum perforatum*], Chaparral [*Larrea tridentate*], Germander [*Teucrium chamaedrys*])<br>Alcohol use<br>Pregnancy<br>For NVP-Associated Hepatic Events in Adults:<br>• Female with pre-NVP CD4 count >250 cells/mm$^3$<br>• Male with pre-NVP CD4 count >400 cells/mm$^3$<br>• Population- specific HLA types[a]<br>• Higher drug concentrations for PIs, particularly TPV. | Prevention:<br>• Avoid concomitant use of hepatotoxic medications.<br>• If hepatic enzymes are elevated >5 to 10 times ULN or chronic liver disease, most clinicians would avoid NVP.<br>Monitoring:<br>*For ARVs Other Than NVP:*<br>• Obtain AST and ALT at baseline and thereafter at least every 3–4 months, or more frequently in at-risk patients (e.g., HBV- or HCV-coinfection or elevated baseline AST and ALT).<br>*For NVP:*<br>• Obtain AST and ALT at baseline, at 2 and 4 weeks, and then every 3 months. | • Evaluate for other infectious and non-infectious causes and monitor closely.<br>Asymptomatic:<br>• Potentially offending ARVs should be discontinued if ALT or AST is > 5x ULN<br>Symptomatic:<br>• Discontinue all ARVs and other potentially hepatotoxic drugs.<br>If a patient experiences hepatitis attributed to NVP, it should be permanently discontinued.<br>• Consider viral causes of hepatitis: HAV, HBV, HCV, EBV, and CMV. |

## Table 13e. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Hepatic Events

(Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 2)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Indirect Hyperbilirubinemia** | IDV, ATV (with either RTV or COBI) | Onset:<br>• First months of therapy<br>Presentation:<br>• May be associated with jaundice or asymptomatic<br>• Direct bilirubin may be normal or slightly elevated when levels of indirect bilirubin are very high.<br>• Normal AST and ALT. | In long-term follow-up, 9% of children receiving ATV had at least 1 total bilirubin level > 5x ULN and 1.4% experienced jaundice. | N/A | Monitoring:<br>• No ongoing monitoring needed. After an initial rise over the first few months of therapy, unconjugated bilirubin levels generally stabilize; in some patients, levels improve over time. | • Isolated indirect hyperbilirubinemia is not indication for cessation of potentially offending ARV<br>• Psychological impact of jaundice should be evaluated and alternative agents considered |
| **Non-Cirrhotic Portal Hypertension** | ddI, d4T | Onset:<br>• Generally after years of therapy<br>Presentation:<br>• GI bleeding, esophageal varices, hypersplenism<br>• Mild elevations in AST and ALT, moderate increases in ALP, and pancytopenia (because of hypersplenism)<br>• Liver biopsy may reveal a variety of findings, most commonly nodular regenerative hyperplasia or hepatoportal sclerosis. | Rare | Prolonged exposure to ARV therapy, especially ddI and the combination of ddI and d4T | Monitoring:<br>• No specific monitoring | • Discontinue potentially offending agents.<br>• Manage complications of GI bleeding and esophageal varices. |

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

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

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## Table 13f. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Insulin Resistance, Asymptomatic Hyperglycemia, Diabetes Mellitus (Last updated April 27, 2017; last reviewed April 27, 2017)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Insulin Resistance, Asymptomatic Hyperglycemia, DM**[a] | ZDV<br>d4T<br>ddI<br>LPV/r<br>IDV<br>Rarely other PIs | Onset:<br>Weeks to months after beginning therapy<br>Presentation:<br>• Asymptomatic fasting hyperglycemia (possibly in the setting of lipodystrophy), metabolic syndrome, or growth delay<br>• Symptomatic DM (rare) | Insulin Resistance<br>*ARV-Treated Children:*<br>• 6% to 12%<br>Impaired Fasting Glucose<br>*ARV-Treated Children:*<br>• 0% to 7%<br>Impaired Glucose Tolerance<br>*ARV-Treated Children:*<br>• 3% to 4%<br>DM<br>*ARV-Treated Children:*<br>• 0.2 per 100-person-years | Risk Factors for Type 2 DM:<br>• Lipodystrophy<br>• Metabolic syndrome<br>• Family history of DM<br>• High BMI (obesity) | Prevention:<br>• Lifestyle modification<br>• Avoid ZDV, d4T, ddI when possible.<br>Monitoring:<br>• Monitor for signs of DM, change in body habitus, acanthosis nigricans.<br>*Obtain RPG Levels at:*<br>• Initiation of ARV therapy<br>• 3–6 months after therapy initiation<br>• Once a year thereafter<br>*For RPG ≥140 mg/dL:*<br>• Obtain FPG performed after 8-hour fast and consider referral to endocrinologist. | Counsel on lifestyle modification (e.g., a diet low in saturated fat, cholesterol, transfat, and refined sugars; increased physical activity; cessation of smoking); consultation with dietician.<br>Change NRTI backbone (e.g., from ZDV, d4T, or ddI to TAF, TDF, or ABC).<br>For Either RPG ≥200 mg/dL plus Symptoms of DM or FPG ≥126 mg/dL:<br>• Patient meets diagnostic criteria for DM; consult endocrinologist.<br>FPG 100–125 mg/dL:<br>Impaired FPG is suggestive of insulin resistance; consult endocrinologist.<br>FPG <100 mg/dL:<br>*Normal FPG, but Does Not Exclude Insulin Resistance:*<br>• Recheck FPG in 6–12 months. |

[a] 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 ≥126 mg/dL, a random PG ≥200 mg/dL in a patient with hyperglycemia symptoms, an HgbA1C of ≥6.5%, or a 2-hour PG after OGTT ≥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 random and fasting plasma glucose 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; IDV = indinavir; 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 13g. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lactic Acidosis (Last updated April 27, 2017; last reviewed April 27, 2017)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Lactic Acidosis** | NRTIs, in particular, d4T and ddI (highest risk when co-administered) | Onset:<br>• 1–20 months after starting therapy (median onset 4 months in 1 case series)<br>Presentation<br>*Usually Insidious Onset of a Combination of Signs and Symptoms:*<br>• Generalized fatigue, weakness, and myalgias<br>• Vague abdominal pain, weight loss, unexplained nausea or vomiting<br>• Dyspnea<br>• Peripheral neuropathy<br>**Note:** Patients may present with acute multi-organ failure (e.g., fulminant hepatic, pancreatic, respiratory failure). | Chronic, Asymptomatic Mild Hyperlactatemia (2.1–5.0 mmol/L)<br>*Adults:*<br>• 15% to 35% of adults receiving NRTI therapy for longer than 6 months<br>*Children:*<br>• 29% to 32%<br>Symptomatic Severe Hyperlactatemia (>5.0 mmol/L)<br>*Adults:*<br>• 0.2% to 5.7%<br>Symptomatic Lactic Acidosis/Hepatic Steatosis:<br>• Rare in all age groups (1.3–11 episodes per 1000 person-years; increased incidence with the use of d4T/ddI when co-administered), but associated with a high fatality rate (33% to 58%) | Adults:<br>• Female gender<br>• High BMI<br>• Chronic HCV infection<br>• African-American race<br>• Prolonged NRTI use (particularly d4T and ddI)<br>• Co-administration of ddI with other agents (e.g., d4T, TDF, RBV, tetracycline)<br>• Co-administration of TDF with metformin<br>• Overdose of propylene glycol<br>• CD4 count <350 cells/mm$^3$<br>• Acquired riboflavin or thiamine deficiency<br>• Possibly pregnancy<br>Preterm Infants or Any Neonates before Post-Menstrual Age of 42 Weeks and a Postnatal Age of ≥14 Days has Been Attained:<br>• Exposure to propylene glycol (e.g., present as a diluent in LPV/r oral solution) due to diminished ability to metabolize propylene glycol, thereby leading to accumulation and potential adverse events. | Prevention:<br>• d4T and ddI should both be avoided individually; co-administration of d4T and ddI is contraindicated (no exception).<br>• 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.<br>• Monitor for clinical manifestations of lactic acidosis and promptly adjust therapy.<br>Monitoring<br>*Asymptomatic:*<br>• Measurement of serum lactate is not recommended.<br>*Clinical Signs or Symptoms Consistent with Lactic Acidosis:*<br>• Obtain blood lactate level.[a] Additional diagnostic evaluations should include serum bicarbonate and anion gap and/or arterial blood gas, amylase and lipase, serum albumin, and hepatic transaminases. | Lactate 2.1–5.0 mmol/L (Confirmed with Second Test):<br>• Replace ddI and d4T with other ARVs.<br>• As an alternative, temporarily discontinue all ARVs while conducting additional diagnostic workup.<br>Lactate >5.0 mmol/L (Confirmed with Second Test)[b] or >10.0 mmol/L (Any 1 Test):<br>• Discontinue all ARVs.<br>• Provide supportive therapy (IV fluids; some patients may require sedation and respiratory support to reduce oxygen demand and ensure adequate oxygenation of tissues).<br>Anecdotal (Unproven) Supportive Therapies:<br>• Bicarbonate infusions, THAM, high-dose thiamine and riboflavin, oral antioxidants (e.g., L-carnitine, co-enzyme Q10, vitamin C)<br>Following resolution of clinical and laboratory abnormalities, resume therapy, either with an NRTI-sparing regimen or a revised NRTI-containing regimen instituted with caution, using NRTIs less likely to inhibit mitochondria (ABC or TDF preferred; possibly FTC or 3TC), and monthly monitoring of lactate for at least 3 months. |

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

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

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

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## Table 13h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)

| Adverse Effects | Associated ARVs | Onset/ Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Lipodystrophy (Fat Maldistribution)** General Information | See below for specific associations. | Onset:<br>• Trunk and limb fat initially increase; peripheral fat wasting may not appear for 12 to 24 months after ART initiation. | Varies greatly depending upon measure and comparator group.<br>Adults:<br>• Up to 93%<br>Children:<br>• Up to 34% | Genetic predisposition<br>Puberty<br>HIV-associated inflammation<br>Older age<br>Longer duration of ART<br>Body habitus | See below. | See below.<br>A regimen review with consideration of changing the regimen should be considered, whenever present.<br>Improvement following regimen change is variable, may take months to several years, or may not occur at all. |
| **Central Lipohypertrophy** or **Lipoaccumulation** | Can occur in the absence of ART, but most associated with PIs and EFV. | Presentation:<br>• 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. | Adults:<br>• Up to 93%<br>Children:<br>• Up to 27% | Obesity before initiation of therapy<br>Sedentary lifestyle | Prevention:<br>• Calorically appropriate low-fat diet and exercise<br>Monitoring:<br>• BMI measurement<br>• Body circumference and waist-hip ratio | Calorically appropriate healthy diet low in saturated fats and simple carbohydrates, and exercise, especially strength training<br>Smoking cessation (if applicable) to decrease future CVD risk<br>Consider switching from PIs and EFV to an INSTI.<br>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:<br>• Recombinant human growth hormone<br>• Growth hormone-releasing hormone<br>• Metformin<br>• Thiazolidinediones<br>• Recombinant human leptin<br>• Anabolic steroids<br>• Liposuction |

## Table 13h. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Lipodystrophy, Lipohypertrophy, Lipoatrophy (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)

| Adverse Effects | Associated ARVs | Onset/ Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **Facial/Peripheral Lipoatrophy** | Most associated with thymidine analogue NRTIs (d4T > ZDV) | Presentation:<br>• Thinning of subcutaneous fat in face, buttocks, and extremities, measured as decrease in trunk/ limb fat by DXA or triceps skinfold thickness. Preservation of lean body mass distinguishes lipoatrophy from HIV-associated wasting. | Adults:<br>• Up to 59%<br>Children:<br>• Up to 47%<br>• Risk lower (up to 15%) in patients not treated with d4T or ZDV. | Underweight before ART | Prevention:<br>• Avoid use of d4T and ZDV.<br>Monitoring:<br>• Patient self-report and physical exam are the most sensitive methods of monitoring lipoatrophy. | Replace d4T (no longer recommended) or ZDV with other NRTIs if possible.<br>Data are Insufficient to Allow the Panel to Safely Recommend Use of Any of the Following Modalities in Children:<br>• Injections of poly-L-lactic acid<br>• Recombinant human leptin<br>• Autologous fat transplantation<br>• Thiazolidinediones |

**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 13i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects

**(Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 2)**

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Urolithiasis/ Nephrolithiasis** | ATV, IDV<br><br>DRV causes crystalluria but is not associated with nephrolithiasis. | Onset:<br>• Weeks to months after starting therapy<br><br>Clinical Findings:<br>• Crystalluria, hematuria, pyuria, flank pain, sometimes increased creatinine | ATV-related nephrolithiasis occurs in <10%.<br><br>IDV-related higher (29%) in children than adults (12.4%) | In adults, elevated urine pH (>5.7)<br><br>Unknown in children | Prevention:<br>• Maintain adequate hydration.<br>• IDV is not FDA-approved for use in children and should be avoided.<br><br>Monitoring:<br>• Obtain urinalysis at least every 6–12 months. | Provide adequate hydration and pain control; consider using alternative ARV. If on IDV, discontinue. |
| **Renal Dysfunction** | TDF | Onset:<br>• Variable; in adults, weeks to months after initiation of therapy.<br>• Hypophosphatemia appears at a median of 18 months.<br>• Glucosuria may have onset after a year of therapy.<br>• Abnormal urine protein/osmolality ratio may be an early indicator.<br><br>Presentation:<br>*More Common:*<br>• Increased serum creatinine, proteinuria, normoglycemic glucosuria. Hypophosphatemia, usually asymptomatic; may present with bone and muscle pain, weakness.<br><br>*Less Common:*<br>• Renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis, nephrogenic diabetes insipidus with polyuria | Adults:<br>• Approximately 2% with increased serum creatinine<br>• Approximately 0.5% with severe renal complications<br><br>Children:<br>• Approximately 4% with hypophosphatemia or proximal tubulopathy; higher with prolonged TDF therapy, in advanced HIV infection or concomitant use of ddI | Risk May Be Increased in Children with:<br>• Age >6 years<br>• Black race, Hispanic/ Latino ethnicity<br>• Advanced HIV infection<br>• Hypertension<br>• Diabetes<br>• Concurrent use of ddI or PIs (especially LPV/r), and preexisting renal dysfunction<br>• Risk increases with longer duration of TDF treatment. | Monitor urine protein and 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.<br><br>In the presence of persistent proteinuria or glucosuria, or for symptoms of bone pain or muscle pain or weakness, also measure serum phosphate.<br><br>Because toxicity risk increases with duration of TDF treatment, frequency of monitoring should not decrease with time. | If TDF is the likely cause, consider using alternative ARV. TAF has significantly less toxicity than TDF. |

## Table 13i. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Nephrotoxic Effects
**(Last updated April 27, 2017; last reviewed April 27, 2017)** (page 2 of 2)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Elevation in Serum Creatinine** | DTG, COBI, RPV | Onset:<br>• Within a month of starting treatment<br>Presentation:<br>• Asymptomatic. These drugs decrease renal tubular secretion of creatinine, leading to an increase in measured serum creatinine without a true change in eGFR. | Common<br>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. | N/A | Monitor serum creatinine. Assess for renal dysfunction if serum creatinine increases by >0.4 mg/dL or increases are ongoing with time. | No need to change therapy.<br>Reassure patient about the benign nature of the laboratory abnormality. |

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

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## Table 13j. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Osteopenia and Osteoporosis (Last updated April 27, 2017; last reviewed April 27, 2017)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Osteopenia and Osteoporosis** | Any ART regimen<br><br>Specific Agents of Possible Concern:<br>• TDF<br>• PIs, especially LPV/r | Onset:<br>• Any age; decrease in BMD usually seen early after initiation of ART.<br><br>Presentation:<br>• Most commonly asymptomatic<br>• Rarely presents as osteoporosis; a clinical diagnosis defined by evidence of bone fragility (e.g., fracture with minimal trauma). | BMD *z* Score Less Than -2.0:<br>• <10% in U.S. cohorts<br>• Approximately 20% to 30% in international cohorts | Longer duration and greater severity of HIV disease<br>Growth or pubertal delay<br>Low BMI<br>Lipodystrophy<br>Non-black race<br>Smoking<br>Prolonged systemic corticosteroid use<br>Medroxyprogesterone use<br>Limited weight-bearing exercise | Prevention:<br>• Ensure sufficient calcium intake and vitamin D sufficiency.<br>• Encourage weight-bearing exercise.<br>• Minimize modifiable risk factors (e.g., smoking, low BMI, use of steroids or medroxyprogesterone).<br><br>Monitoring:<br>• Assess nutritional intake (calcium, vitamin D, and total calories).<br>• Consider measuring serum 25-OH-vitamin D level.[a]<br>• DXA.[b] | Same options as for prevention.<br><br>Consider change in ARV regimen (e.g., changing TDF to TAF).<br><br>Role of bisphosphonates not established in children with HIV infection. |

[a] Some experts would periodically measure 25-OH-vitamin D, especially in urban youth with HIV infection, because in that population, the prevalence of vitamin D insufficiency is high.

[b] Until more data are available about the long-term effects of TDF on bone mineral acquisition in childhood, some experts would obtain a DXA at baseline and every 6 to 12 months for prepubertal children and children in early puberty who are initiating treatment with TDF. DXA could also be considered in adolescent women on TDF and medroxyprogesterone and in 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; LPV/r = lopinavir/ritonavir; PI = protease inhibitor; TDF = tenofovir disoproxil fumarate, TAF= tenofovir alafenamide

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### Osteopenia and Osteoporosis


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## Table 13k. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Peripheral Nervous System Toxicity (Last updated April 27, 2017; last reviewed April 27, 2017)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency[a] | Risk Factors | Prevention/ Monitoring | Management |
|---|---|---|---|---|---|---|
| **ARV Toxic Neuropathy**[b] | d4T, ddI<br>PIs | Onset:<br>Weeks to months<br>Presentation:<br>• Decreased sensation<br>• Aching, burning, painful numbness<br>• Hyperalgesia<br>• Allodynia<br>• Decreased or absent ankle reflexes<br>*Distribution:*<br>• Bilateral soles of feet, ascending to legs and fingertips | Children:<br>• Around 1% overall<br>• d4T—10% to 25%<br>Adults:<br>• d4T—up to 50% | • Pre-existing neuropathy<br>• Elevated triglyceride levels<br>• Poor nutrition<br>• More advanced HIV disease<br>• Concomitant use of other neurotoxic agents (e.g., INH)<br>• Some mitochondrial DNA haplogroups may have increased risk. | Avoid use of d4T and ddI.<br>Monitor for symptoms and signs of peripheral neuropathy. | Discontinue offending agent.<br>Topical capsaicin 8% may be helpful.<br>Consider referral to a neurologist.<br>Data are insufficient to allow the Panel to recommend use of any of the following modalities: tricyclic antidepressants, gabapentin, gregabalin, mexiletine, Lamotrigine, and acupuncture or other complementary approaches |

[a] Peripheral neuropathy may be underreported in children because symptoms are difficult to evaluate in young children.

[b] HIV infection itself may cause a distal sensory neuropathy that is phenotypically identical to ARV toxic neuropathy.

**Key to Acronyms:** ARV = antiretroviral; d4T = stavudine; ddI = didanosine; INH = isoniazid; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

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## Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 1 of 4)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **Rash** | Any ARV can cause rash | Onset:<br>• First few days to weeks after starting therapy<br>Presentation:<br>• Most rashes are mild-to-moderate, diffuse maculopapular eruptions.<br>**Note:** A rash can be the initial manifestation of systemic hypersensitivity (see Systemic HSR, SJS/TEN/EM Major) | Common (>10% Adults and/or Children):<br>• NVP, EFV, ETR, FPV, FTC<br>Less Common (5% to 10%):<br>• ABC, DRV, TPV, TDF<br>Unusual (2% to 4%):<br>• LPV/r, RAL, MVC, RPV | • Sulfonamide allergy is a risk factor for rash with PIs containing a sulfonamide moiety (FPV, DRV, and TPV)<br>• Polymorphisms in CYP2B6 and multiple HLA loci may confer increased risk of rash with NVP. | When Starting NVP or Restarting After Interruptions >14 Days:<br>• Utilize once-daily lead-in dosing (see NVP section).[a]<br>• Avoid the use of systemic corticosteroids during NVP dose escalation.<br>• Assess patient for rash severity, mucosal involvement, and other signs of systemic reaction. | Mild-to-Moderate Maculopapular Rash Without Systemic or Mucosal Involvement:<br>• Most will resolve without intervention; ARVs can be continued while monitoring.[a]<br>• Antihistamines may provide some relief.<br>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):<br>• Manage as SJS/TEN/EM major (see below).<br>Rash in Patients Receiving NVP:<br>• Given elevated risk of HSR, measure hepatic transaminases.<br>• If hepatic transaminases are elevated, NVP should be discontinued and not restarted (see HSR-NVP). |
| | ENF | Onset:<br>• First few days to weeks after starting therapy<br>Presentation:<br>• Local injection site reactions with pain, erythema, induration, nodules and cysts, pruritus, ecchymosis. Often multiple reactions at the same time | Adults and Children:<br>• >90% | Unknown | • Routinely assess patient for local reactions.<br>• Rotate injection sites.<br>• Massage area after injection. | • Continue the agent as tolerated by the patient.<br>• Ensure patient is injecting as per instructions.<br>• Rotate injection sites. |

## Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 2 of 4)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **SJS/TEN/EM Major** | Many ARVs, especially NNRTIs (see Estimated Frequency column) | Onset:<br>• First few days to weeks after initiating therapy<br>Presentation:<br>• 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. | Infrequent:<br>• NVP (0.3%), EFV (0.1%), ETR (<0.1%)<br>Case Reports:<br>• FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV, RAL | Adults:<br>• Female gender<br>• Race/ethnicity (black, Asian, Hispanic) | When Starting NVP or Restarting After Interruptions >14 Days:<br>• Utilize once-daily lead-in dosing (see NVP section).[a]<br>• Counsel families to report symptoms as soon as they appear. | • Discontinue all ARVs and other possible causative agents such as TMP-SMX.<br>• Provide intensive supportive care, IV hydration, aggressive wound care, pain management, antipyretics, parenteral nutrition, and antibiotics as needed in case of superinfection.<br>• Corticosteroids and/or IVIG are sometimes used, but use of each is controversial.<br>• Do not reintroduce the offending medication.<br>• In case of SJS/TEN/EM major with one NNRTI, many experts would avoid use of other NNRTIs. |
| **DRESS** | EFV, ETR, NVP, RAL, RPV, DRV | Onset:<br>• 1–8 weeks<br>Presentation:<br>• Fever<br>• Lymphadenopathy<br>• Facial swelling<br>• Morbilliform to polymorphous rash<br>• Peripheral eosinophilia<br>• Atypical circulating lymphocytes<br>• Internal organ involvement (particularly liver and/or renal) | Rare | Unknown | • Obtain CBC, AST, ALT and creatinine in patient presenting with suggestive symptoms. | • Discontinue all ARVs and other possible causative agents such as TMP-SMX.<br>• Role for steroids unclear; suggest consultation with specialist.<br>• Supportive care for end-organ disease<br>• Do not reintroduce the offending medication. |

## Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 3 of 4)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **HSR**<br><br>With or without skin involvement and excluding SJS/TEN | ABC | Onset<br>*With First Use:*<br>• Within first 6 weeks<br>*With Reintroduction:*<br>• Within hours<br>Presentation:<br>• Symptoms include high fever, diffuse skin rash, malaise, nausea, headache, myalgia, arthralgia, diarrhea, vomiting, abdominal pain, pharyngitis, respiratory symptoms (e.g., dyspnea).<br>• Symptoms worsen to include hypotension and vascular collapse with continuation. With rechallenge, symptoms can mimic anaphylaxis. | 2.3% to 9% (varies by racial/ethnic group). | • HLA-B*5701 (HSR very uncommon in people who are HLA-B*5701-negative); also HLA-DR7, HLA-DQ3.<br>• HSR risk is higher in those of white race compared to those of black or East Asian race. | • Screen for HLA-B*5701. **ABC should not be prescribed if HLA-B*5701 is present.** The medical record should clearly indicate that ABC is contraindicated.<br>• When starting ABC, counsel patients and families about the signs and symptoms of HSR to ensure prompt reporting of reactions. | • Discontinue ARVs and investigate for other causes of the symptoms (e.g., a concurrent viral illness).<br>• Treat symptoms as necessary.<br>• Most symptoms resolve within 48 hours after discontinuation of ABC.<br>• Do not rechallenge with ABC even if the patient is HLA-B*5701-negative. |

## Table 13I. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations—Rash and Hypersensitivity Reactions (Last updated April 27, 2017; last reviewed April 27, 2017) (page 4 of 4)

| Adverse Effects | Associated ARVs | Onset/Clinical Manifestations | Estimated Frequency | Risk Factors | Prevention/Monitoring | Management |
|---|---|---|---|---|---|---|
| **HSR**<br>With or without skin involvement and excluding SJS/TEN | NVP | Onset:<br>• Most frequent in the first few weeks of therapy but can occur through 18 weeks.<br>Presentation:<br>• Flu-like symptoms (including nausea, vomiting, myalgia, fatigue, fever, abdominal pain, jaundice) with or without skin rash that may progress to hepatic failure with encephalopathy. | 4% (2.5% to 11%) | Adults:<br>• Treatment-naive with higher CD4 count (>250 cells/mm$^3$ in women; >400 cells/mm$^3$ in men).<br>• Female gender (risk is 3-fold higher in females compared with males).<br>Children:<br>• NVP hepatotoxicity and HSR are less common in pre-pubertal children than in adults. The PREDICT Study showed a 2.65 times higher risk of overall NVP toxicity (rash, hepatotoxicity, hypersensitivity) in children with CD4 ≥15% compared to children with CD4 <15%. | When Starting NVP or Restarting After Interruptions >14 Days:<br>• 2-week lead-in period with once-daily dosing then dose escalation to twice daily as recommended may reduce risk of reaction.[a]<br>• Counsel families about signs and symptoms of HSR to ensure prompt reporting of reactions.<br>• 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.<br>• Avoid NVP use in women with CD4 counts >250 cells/mm$^3$ and in men with CD4 counts >400 cells/mm$^3$ unless benefits outweigh risks.<br>• Do not use NVP in PEP. | • Discontinue ARVs<br>• Consider other causes for hepatitis and discontinue all hepatotoxic medications.<br>• Provide supportive care as indicated and monitor patient closely<br>• 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. |
| | ENF, ETR | Onset:<br>• Any time during therapy.<br>Presentation:<br>• Symptoms may include rash, constitutional findings, and sometimes organ dysfunction including hepatic failure. | Rare | Unknown | • Evaluate for hypersensitivity if the patient is symptomatic. | • Discontinue ARVs.<br>• Rechallenge with ENF or ETR is not recommended. |
| | MVC | Rash preceding hepatotoxicity | Rare | Unknown | • Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity. | • Discontinue all ARVs<br>• Rechallenge with MVC is not recommended. |
| | DTG | Rash with hepatic dysfunction | Rare | Unknown | • Obtain AST and ALT in patients with rash or other symptoms of hypersensitivity. | • Discontinue all ARVs.<br>• Rechallenge with DTG is contraindicated. |

[a] 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 consultation with an expert in HIV care should be obtained. **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 cell; ddI = didanosine; DRESS = drug rash with eosinophilia and systemic symptoms; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EM = erythema multiforme; ENF = enfuvirtide; 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; TDF = tenofovir disoproxil fumarate; TEN = toxic epidermal necrolysis; TPV = tipranavir; ZDV = zidovudine

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# Management of Children Receiving Antiretroviral Therapy (Last updated April 27, 2017; last reviewed April 27, 2017)

In the United States, the majority of children living with HIV are receiving antiretroviral therapy (ART), making treatment-experienced children the norm. Changes in 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 on effective ART for simplification or improved adverse event (AE) profile;
2. Recognizing and managing ARV drug toxicity or intolerance (see Management of Medication Toxicity or Intolerance);
3. Recognizing and managing treatment failure; and
4. Considerations about interruptions in therapy.

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

**Panel's Recommendations**

- Children who have sustained virologic suppression on their current regimen should be regularly evaluated for opportunities to change to a new regimen that facilitates adherence, simplifies antiretroviral (ARV) administration, increases ARV potency, and decreases the risk of drug-associated toxicity **(AII)**.
- Past episodes of antiretroviral 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 activity **(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*

Initial ARV regimens are chosen based on safety, pharmacokinetic and efficacy data for drugs available in formulations suitable for the age of the child at initiation of ART. 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 the setting of sustained virologic suppression (e.g., 6–12 months) on their current regimen, changing to a new ARV regimen may be considered in order to permit use of pills instead of liquids, reduce pill burden, allow use of once-daily medications, reduce risk of AEs, and align their regimens with widely used, efficacious adult regimens.[1] Often the changes enhance adherence and improve quality of life.[2]

Several studies have addressed switching ARV regimen components in children with sustained virologic suppression. Based on the NEVEREST 2 study, young children (i.e., 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 LPV/r, provided there is good adherence and no baseline resistance to nevirapine.[3,4] In the NEVEREST 3 study, children ≥3 years of age with a history of exposure to nevirapine and with virologic suppression on LPV/r maintained virologic suppression when switched from LPV/r to efavirenz.[5,6] Similarly, in the NEVEREST 2 study, children switched to a nevirapine regimen showed better immune and growth responses than those continuing a LPV/r regimen.[3] By extrapolation, replacement of LPV/r with an equally potent protease inhibitor (PI) (e.g., darunavir, atazanavir), or an integrase inhibitor (INSTI) (e.g., elvitegravir, raltegravir, dolutegravir) would likely be effective, but that has not been directly studied. Several small studies 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, in small cohorts of children.[7-11] Small studies have shown that children with virologic suppression on certain twice-daily regimens (i.e., abacavir, nevirapine) maintain virologic suppression if changed from twice daily to once daily (see Abacavir and Nevirapine drug sections) but 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 <30kg.[12-15]

Dual and monotherapy protease inhibitor (darunavir/ritonavir, LPV/r, atazanavir/ritonavir) and INSTI (dolutegravir) strategies in adult patients with sustained virologic suppression for the purposes of simplification or reduced toxicity have been attempted with varying success. They are being further explored, but are not currently recommended as a management strategy. Limited studies have been done in children and these strategies cannot be endorsed at this time.[16-20]

Table 14 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, it is important to ensure that a child does not have virologic treatment failure. It is also critical to consider past episodes of ART, 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.[21-25] The evidence supporting many of these ARV changes is indirect, extrapolated from data about drug performance in initial therapy or follow-on therapy after treatment failure. When such changes are made, careful monitoring (e.g., viral load measurement 2–4 weeks after switch to new regimen) is important to ensure that virologic suppression is maintained.

**Table 14: 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[a] (page 1 of 2)**

| ARV Drug(s) | Age | Body Size Attained | Potential ARV Regimen Change | Comment[b] |
|---|---|---|---|---|
| **NRTIs** | | | | |
| **ABC**<br>**Twice Daily** | ≥1 year | Any | ABC once daily | See Abacavir in Appendix A: Pediatric Antiretroviral Drug Information for full discussion. |
| **ZDV or ddI (or d4T[c])** | ≥1 year | N/A | ABC | Once-daily dosing (see Abacavir in Appendix A: Pediatric Antiretroviral Drug Information). Less long-term mitochondrial toxicity. TDF is a reasonable option for children unable to take ABC (HLA B5701 positive) who want to switch to a once-daily regimen. |
| | N/A | >35 kg | TAF or ABC | N/A |
| | Adolescence | Pubertal maturity (i.e., SMR IV or V) | TDF, TAF or ABC | Once-daily dosing. Less long-term mitochondrial toxicity. Coformulation with other ARV drugs can further reduce pill burden. TAF preferred over TDF for lower bone toxicity. |
| **NNRTIs** | | | | |
| EFV | ≥12 years | ≥40 kg | ATV/r<br>DRV/r<br>DTG<br>RPV | Smaller pill (DTG), higher barrier to resistance given concern for adherence challenges developing in adolescents.<br>DRV/r may be administered once daily in children aged ≥12 years without DRV resistance mutations. |

**Table 14: 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[a] (page 2 of 2)**

| ARV Drug(s) | Age | Body Size Attained | Potential ARV Regimen Change | Comment[b] |
|---|---|---|---|---|
| **PIs** | | | | |
| **LPV/r Twice Daily** | ≥1 year | ≥3 kg | RAL<br>ATV/r | Better palatability. Less adverse lipid effect. Lower pill burden. Once-daily dosing (ATV/r). |
| | ≥3 years | N/A | ATV/r<br>EFV<br>RAL<br>DTG (weighing ≥30 kg)<br>EVG (weighing ≥25 kg) | Once-daily dosing (EFV and ATV/r). Better palatability. Less adverse lipid effect. See Efavirenz in Appendix A: Pediatric Antiretroviral Drug Information regarding concerns about dosing for children aged <3 years. |
| | ≥12 years | ≥40 kg | DRV/r<br>ATV/r<br>DTG<br>RPV | Once-daily dosing possible. Lower pill burden. |
| **Other** | | | | |
| **Any Multi-Pill and/or Twice-Daily Regimen** | Adolescence | For regimens with TDF: pubertal maturity (i.e., SMR IV or V) | <u>Co-formulated</u>:<br>• TDF/FTC/EFV<br>• TDF/FTC/EVG/COBI<br>• TAF/FTC/EVG/COBI (weighing ≥35 kg)<br>• TDF/FTC/RPV<br>• TAF/FTC/RPV (weighing ≥35 kg)<br>• ABC/3TC/DTG (weighing ≥40 kg)<br>• TAF/FTC plus DTG | Once-daily dosing. Single pill. Alignment with adult regimens. TAF/FTC plus DTG may be more desirable because of small pill sizes even though it increases pill burden to 2 pills instead of 1.<br><br>TAF-based regimens can be used with adolescents weighing ≥35 kg. Use ABC/3TC/DTG for adolescents weighing ≥40kg |

[a] This list is not exhaustive in that it does not necessarily list all potential options, but instead, shows examples of what kinds of changes can be made.

[b] Comments relevant to the potential ARV change listed. Does not include all relevant information. Please refer to individual drug tables for full information.

[c] Because of concerns about long-term adverse events, d4T should be replaced with a safer drug even before sustained virologic suppression is achieved (see Stavudine in Appendix A: Pediatric Antiretroviral Drug Information).

**Key to Acronyms:** 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; 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 (Tanner stage); TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

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## Recognizing and Managing Antiretroviral Treatment Failure (Last updated April 27, 2017; last reviewed April 27, 2017)

**Panel's Recommendations**

- The causes of virologic 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 antiretroviral (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 2, but preferably 3, 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† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

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

## *Categories of Treatment Failure*

Treatment failure can be categorized as virologic failure, immunologic failure, clinical failure, or some combination of the three. Immunologic failure refers to a suboptimal immunologic response to therapy or an immunologic decline while on therapy, but there is no standardized definition. Clinical failure is defined as the occurrence of new opportunistic infections 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) using 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 ≥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. Because infants with high plasma viral loads at initiation of therapy occasionally take longer than 6 months to achieve virologic suppression, some experts continue the treatment regimen for infants receiving ritonavir-boosted (LPV/r)-based therapy if viral load is declining but is still ≥200 copies/mL at 6 months and monitor closely for continued decline to virologic suppression soon thereafter.[1] However, ongoing non-suppression—especially with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens—increases the risk of drug resistance.[2,3] There is controversy regarding the clinical implications of HIV RNA levels between the LLD and <200 copies/mL in patients on antiretroviral therapy (ART). Adults with HIV who have detectable viral loads and a quantified result <200 copies/mL after 6 months of ART generally achieve virologic suppression without regimen change.[4-6] However, some studies in adults have found that repeated viral loads of 50 to <200 copies/mL may be associated with an increased risk of later virologic failure.[7,8] Blips—defined as isolated episodes of plasma viral load detectable at low levels (i.e., <500 copies/mL) followed by return to viral suppression—are common and not generally reflective of virologic failure.[9-11] However, repeated or persistent plasma viral load detection ≥200 copies/mL (especially if >500 copies/mL) after having achieved virologic suppression usually represents virologic failure.[6,11-13]

### Poor Immunologic Response Despite Virologic Suppression

Poor immunologic response despite virologic suppression is uncommon in children.[14] 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$^3$), even if virologic suppression occurs more promptly. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur.

The first considerations in cases of poor immunologic response despite virologic suppression are to exclude laboratory error in CD4 or viral load measurements and to 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 result in lower CD4 values is necessary (see Table 15).

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.[15-17] In a study of 933 children aged ≥5 years who received ART that resulted in virologic suppression, 348 (37%) had CD4 cell counts <500 cells/mm$^3$ at ART initiation, including 92 (9.9%) with CD4 cell counts <200 cells/mm$^3$. After 1 year of virologic suppression, only 7 (1% of the cohort) failed to reach a CD4 cell count ≥200 cells/mm$^3$ and 86% had CD4 cell counts >500 cells/mm$^3$. AIDS-defining events were uncommon overall (1%) but occurred in children who did and did not achieve improved CD4 cell counts.[14]

Several drugs (e.g., corticosteroids, chemotherapeutic agents) and other conditions (e.g., hepatitis C virus, tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis) 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 other agents and treating other conditions that could impair CD4 recovery. The Panel 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. One of the most important reasons for new or recurrent opportunistic conditions—despite achieving virologic suppression and immunologic restoration/preservation within the first months of ART—is immune reconstitution inflammatory syndrome (IRIS), which does not represent ART failure and does not generally require discontinuation of ART.[18,19] 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.[20] 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 tuberculosis, 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.[14] Although such cases are rare, they may represent ART clinical failure and suggest that improvement in CD4 values may not necessarily represent normalization of 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 the strategy are mixed.[21,22]

**Table 15. Discordance Among Virologic, Immunologic, and Clinical Responses**

| **Differential Diagnosis of Poor Immunologic Response Despite Virologic Suppression** |
|---|
| Poor Immunologic Response Despite Virologic Suppression and Good Clinical Response: |
| • Lab error (in CD4 or viral load result) |
| • Misinterpretation of normal, age-related CD4 decline (i.e., immunologic response not actually poor) |
| • Low pretreatment CD4 cell count or percentage |
| • Adverse effects of use of ZDV or the combination of TDF and didanosine |
| • Use of systemic corticosteroids or chemotherapeutic agents |
| • Conditions that can cause low CD4 values, such as HCV, TB, malnutrition, Sjogren's syndrome, sarcoidosis, and syphilis |
| Poor Immunologic and Clinical Responses Despite Virologic Suppression: |
| • Lab error |
| • Falsely low viral load result for HIV strain/type not detected by viral load assay (HIV-1 non-M groups, non-B subtypes; HIV-2) |
| • Persistent immunodeficiency soon after initiation of ART but before ART-related reconstitution |
| • Primary protein-calorie malnutrition |
| • Untreated tuberculosis |
| • Malignancy |
| **Differential Diagnosis of Poor Clinical Response Despite Adequate Virologic and Immunologic Responses** |
| • IRIS |
| • Previously unrecognized preexisting infection or condition (e.g., TB, malignancy) |
| • Malnutrition |
| • Clinical manifestations of previous organ damage: brain (e.g., strokes, vasculopathy), lungs (e.g., bronchiectasis) |
| • New clinical event due to non-HIV illness or condition |
| • New, otherwise unexplained HIV-related clinical event (treatment failure) |

**Key to Acronyms:** ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HCV = hepatitis C virus; IRIS = immune reconstitution inflammatory syndrome; TB = tuberculosis; 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 suspicion of virologic treatment failure should include evaluation of adherence to therapy and medication intolerance, confirmation that prescribed dosing is correct 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 Antiretroviral Drug-Resistance Testing in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). 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 Antiretroviral Drug-Resistance Testing in the Adult and Adolescent Antiretroviral Guidelines). An approach to identifying resistance in this situation is to restart the prior medications while emphasizing adherence, and 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, and virologic suppression may be achieved with continuation of the PI-based regimen accompanied by adherence improvement measures.[23,24]

In some cases, the availability of a new regimen for which the convenience (e.g., single fixed-dose tablet once daily) is anticipated to address the main barrier to adherence may make it reasonable to change to this new regimen 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).

### Virologic Treatment Failure with Viral Drug Resistance Identified

After reaching a decision that a change in therapy is needed, a clinician should attempt to identify at least 2, but preferably 3, fully active ARV agents from at least 2 different classes on the basis of resistance test results, prior ARV exposure, acceptability to the patient, and likelihood of adherence.[25-29] 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 because of the presence of drug-resistance mutations that confer cross-resistance within a drug class.

A change to a new regimen must include an extensive discussion of treatment adherence and potential toxicity with a patient in an age- and development-appropriate manner and with a patient's caregivers. 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.[30]

## *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 16, 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 has failed initial therapy with an NNRTI-based regimen, a change to a PI-based regimen is generally effective. Since there is no evidence of better outcomes (from studies in adults) of a boosted PI regimen including raltegravir compared to a boosted PI regimen containing 2 NRTIs, most children failing an initial NNRTI-based regimen should be changed to a regimen of a boosted PI plus 2 NRTIs.[31,32] Limited data support use of 2 NRTIs plus an INSTI following failure of an NNRTI-based regimen,[33,34] but there is concern about this approach (especially with INSTIs with lower barrier to resistance such as raltegravir), because children failing NNRTI-based regimens often have substantial NRTI resistance.[35] Resistance to the NNRTI nevirapine results in cross-resistance to the NNRTI efavirenz, and vice versa. However, 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 fails initial therapy with a PI-based regimen, there is often limited resistance detected,[35,36] 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.[37-39] Darunavir/r-based therapy has also been used.[40,41] Based on more limited data, a change to an INSTI-based regimen can be effective.[33,42]

The availability of newer drugs in existing classes and newer classes of drugs increases the likelihood of finding 3 active drugs, even for children with extensive drug resistance (see Table 16). As discussed, INSTI-based regimens are increasingly used for children who have failed NNRTI- or PI-based regimens.[33,42] The INSTI with the greatest experience in children is raltegravir but dolutegravir (see 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 failed raltegravir-based therapy. Maraviroc, a CCR5 antagonist, provides a new class but many treatment-experienced children already harbor X4-tropic virus that precludes its use.[43] Regimens including an INSTI and potent, boosted PI plus or minus etravirine have been effective in small studies of extensively ARV-experienced patients with multi-class drug resistance.[44-47] It is important to review individual drug profiles for information about drug interactions and dose adjustment when devising a regimen for children with multi-class 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]). Limited data in adults suggest that continuation of lamivudine can contribute to suppression of HIV replication despite the presence of lamivudine resistance mutations and can maintain lamivudine mutations (184V) that can partially reverse the effect of other mutations conferring resistance to zidovudine, stavudine, and tenofovir disoproxil fumarate.[48-50] 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). New drugs should be used in combination with at least 1, and ideally 2, additional active agents.

Enfuvirtide has been Food and Drug Administration-approved for treatment-experienced children aged ≥6 years but must be administered by subcutaneous injection twice daily.[51,52] 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.[53-55] Multidrug regimens (up to 3 PIs and/or 2 NNRTIs) have shown efficacy in a pediatric case series, but they are complex, often poorly tolerated, and subject to unfavorable drug-drug interactions.[56] Availability of newer PIs (e.g., darunavir for children aged ≥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 4 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,[57,58] 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.[58] There are no studies of NRTI-sparing regimens in children with virologic failure and multidrug resistance, but that may be a reasonable option for children with extensive NRTI resistance.

When searching for at least 2 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 be studied or approved in children or may be in clinical development. Information concerning potential clinical trials can be found at http://aidsinfo.nih.gov/clinical_trials 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.[59] 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.[60]

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 and 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.[61] 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. In a trial (IMPAACT P1094) randomizing children harboring the M184V resistance mutation with persistent nonadherence and virologic failure to continue their non-suppressive, non-NNRTI-based ART regimen versus switching to a lamivudine (or emtricitabine) monotherapy holding regimen, children who switched to monotherapy were significantly more likely to experience a 30% decline in absolute CD4 cell count (the primary outcome) over a 28-week period. The median age of the participants was 15 years, the median entry CD4 cell count was 472 cells/mm$^3$, and the median number of interventions that had been used to address nonadherence was 4. Only patients in the lamivudine/emtricitabine arm experienced the primary outcome.[62] Although this was a small study (N = 33), it is the only study ever to randomize patients to continuing non-suppressive ART versus 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[63,64] (see Treatment Interruption).

**Table 16. 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[a]**

| Prior Regimen | New Regimen Options[a] |
|---|---|
| **2 NRTIs plus NNRTI** | • 2 NRTIs plus PI<br>• 2 NRTIs plus INSTI |
| **2 NRTIs plus PI** | • 2 NRTIs plus INSTI<br>• 2 NRTIs plus different RTV-boosted PI<br>• INSTI plus different RTV-boosted PI+/- NNRTI +/- NRTI(s) |
| **2 NRTIs plus INSTI** | • 2 NRTIs plus RTV-boosted PI<br>• DTG (if not used in the prior regimen) + RTV-boosted PI +/- 1-2 NRTIs |
| **Failed Regimen(s) That Included NRTI(s), NNRTI(s), and PI(s)** | • INSTI + 2 NRTIs (if NRTIs are fully active)<br>• INSTI + 2 NRTIs + RTV-boosted PI (if NRTIs are not fully active)<br>• INSTI + RTV-boosted PI plus +/-ETR or RPV +/- NRTI(s) (if minimal NRTI activity) (consider adding T20 and/or MVC if additional active drug[s] needed) |

[a] ARV 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 2, but preferably 3, fully active drugs for durable, 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 adjustment when devising a regimen for children with multi-class drug resistance.** Collaboration with a pediatric HIV specialist is especially important when choosing regimens for children with multi-class 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; T20 = enfuvirtide

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## Considerations About Interruptions in Antiretroviral Therapy (Last updated April 27, 2017, last reviewed April 27, 2017)

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

### *Unplanned Interruptions*

Temporary discontinuation of antiretroviral therapy (ART) may be necessary in some situations, including serious treatment-related toxicity, acute illnesses or planned surgeries that preclude oral intake, or lack of available medication. 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 non-prescribed treatment interruptions suggest that interruptions are common, most patients will experience immunologic decline during the treatment interruption, and most restart therapy.[1-3] In a retrospective study of 483 children in the ANRS French national pediatric cohort, 42% had treatment interruptions of ≥3 months (median 12.1 months), and interruption was associated with lower CD4 T lymphocyte cell (CD4) percentage at 4 years, even in those who restarted therapy.[4] Whether unplanned interruptions occur by accident or necessity (e.g., because of toxicity), all efforts should be made to minimize their duration. Specific guidance on supporting adherence can be found in the section, 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 those randomized to structured treatment interruptions compared with continuous ART.[5] Current Department of Health and Human Services guidelines for adults recommend against planned long-term structured treatment interruptions in adults (see the Adult and Adolescent Guidelines).

In children, there have been fewer studies of long-term structured treatment interruption. In 1 study, children with controlled viral load (i.e., HIV RNA <400 copies/mL for >12 months) were subjected to increasing intervals of treatment interruption. Of 14 children studied, 4 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.[6] However, new drug-resistance mutations were detected in 3 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 continuous therapy (CT) versus treatment interruption with CD4-guided re-initiation of ART.[7] 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 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% (1% to 3%, $P = 0.001$) lower CD4 percentage by 3 years of follow-up; having any interruption of treatment was associated with a trend to increased mortality [hazard ratio: 2.6 (95% CI, 0.7–10.4)].[8] In some populations of children, structured treatment interruption has been more specifically considered. One trial 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 CHER study in South Africa assessed outcomes in infants randomized to deferred ART (initiation driven by Centers for Disease Control and Prevention stage and CD4 status), immediate ART with interruption after 40 weeks, or immediate ART with interruption after 96 weeks.[9,10] While the 2 arms of immediate ART followed by interrupted therapy led to better outcomes compared to 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 percentage >25 with normal growth) were randomized to treatment interruption or to continue ART.[11] 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 had raised the hope that it may be possible to stop or reduce ART in some infants (see Special Considerations for Neonates).[12-14] However, viral rebound eventually appeared in that infant, 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.[15,16] The Panel recommends that treatment of infants who revert to negative serology or negative HIV DNA testing not be interrupted in an attempt to confirm diagnosis or to assess for remission or cure.

**Short-Cycle Treatment Strategies**

One approach, called short cycle therapy (SCT), schedules brief (four day treatment interruptions), rather than waiting for CD4 decline or other adverse events to restart ART. In one proof-of-concept study (ATN015), 32 participants (aged 12–24 years) underwent short cycles of 4 days on/3 days off ART.[17] Participants were receiving protease inhibitor-based ART, had at least 6 months of documented viral suppression below 400 copies/mL and CD4 count above 350 cells/mm$^3$. Participants demonstrated good adherence to the schedule, but 12 (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+ T cell counts. A more recent study suggests that shorter cycles off ART may result in better outcomes. BREATHER (PENTA 16) was a non-inferiority trial that randomized 199 children (aged 8 to 24) years to SCT (5 days on/2 days off) or continuous treatment (CT).[18] Participants were virologically suppressed (viral load <50 copies/mL for >12 months) and receiving efavirenz plus 2 nucleoside reverse transcriptase inhibitors at enrollment. By 48 weeks, 6 participants in the SCT arm and 7 in the CT arm had a confirmed viral load >50 copies/mL [difference -1.2%, 90% CI, -7.3% to 4.9%] and 2 in the SCT group and 4 in the CT group had a confirmed viral load >400 copies/mL (difference -2.1%, 90% CI, -6.2% to 1.9%). Of the 6 participants in the SCT arm with a viral load >50 copies/mL, 5 had resuppression, 3 on the same regimen and 2 with a switch; 2 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 week 48 they found no evidence of increased inflammation in the SCT arm. Participants expressed a strong preference for SCT in a qualitative substudy and in pre- and post-trial questionnaires. In summary, the BREATHER trial suggests that short-cycle treatment may be safe in some adolescents, and yield increased satisfaction that could lead to better long-term adherence. However, additional data are needed about 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, yielding minimal potential benefits, particularly given the lower toxicity of current ARV agents to counterbalance the risks and limited long-term follow-up data. 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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# Role of Therapeutic Drug Monitoring in Management of Pediatric HIV Infection (Last updated April 27, 2017; last reviewed April 27, 2017)

| Panel's Recommendations |
|---|
| • Routine evaluation of plasma concentrations of antiretroviral (ARV) drugs is not generally recommended in the management of children with HIV infection **(BII)**<br>• Targeted therapeutic drug monitoring of ARV drugs in children can be considered in the following scenarios **(BII)**:<br>  • Use of ARV drugs with limited pharmacokinetic data and/or therapeutic experience in children;<br>  • Use of patient pharmacogenetic profile for the selection of the dose of certain ARV drugs (e.g. efavirenz);<br>  • Significant drug-drug and food-drug interactions;<br>  • Suboptimal treatment response (e.g., lack of virologic suppression) in medication-adherent patients;<br>  • Suspected suboptimal absorption, distribution, metabolism, or elimination of the drug; or<br>  • Suspected concentration-dependent drug-associated toxicity. |
| ***Rating of Recommendations:*** *A = Strong; B = Moderate; C = Optional*<br>***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*<br>*† Studies that include children or children/adolescents but not studies limited to postpubertal adolescents* |

The goal of therapeutic drug monitoring (TDM) of antiretroviral (ARV) drugs is to optimize treatment responses and tolerability, and to minimize drug-associated toxicity. TDM may be useful in clinical management with drugs that have a known exposure-response relationship and a relatively narrow therapeutic window of desirable concentrations. The therapeutic window is a range of concentrations that are associated with the greatest likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions in clinical investigations. While many ARV drugs (e.g., most protease inhibitors, first-generation non-nucleoside reverse transcriptase inhibitors, the CCR5 receptor antagonist maraviroc) have target plasma trough concentrations associated with viral efficacy, only a few ARV drugs have drug levels associated with toxicity (e.g., nevirapine and efavirenz). Most TDM targets have been established in adult studies, but several drugs (e.g., lopinavir, nelfinavir, efavirenz, nevirapine) have had target concentrations validated in pediatric studies. The suggested efficacy plasma trough concentrations are generally applicable when resistance testing demonstrates susceptibility of the patient's virus to the particular ARV drug. Table 17 includes data on the efficacy plasma trough concentrations derived from adult clinical trials of the ARV drugs. Historically, most TDM target concentrations for ARV drugs focused on reaching a trough ($C_{trough}$) or minimum plasma concentration ($C_{min}$).[1] Population average $C_{min}$ for all ARV drugs (including newer ARV drugs) can be found in the Food and Drug Administration-approved product labels.

**Table 17. Target Trough Concentrations of Antiretroviral Drugs Relevant to Pediatric Populations**[a]

| Drug | Plasma Trough Concentration (ng/mL) ± Standard Deviation |
|---|---|
| Atazanavir | 2,000±1,000 |
| Darunavir | 2,200±1,100 |
| Fosamprenavir | 2,100 |
| Lopinavir | 5,500±4,000 |
| Nelfinavir | 700±400 |
| Efavirenz | 1,700±1,000 |
| Nevirapine | 4,500±1,900 |
| Etravirine | 300 |
| Tipranavir | 20,000–45,000 |
| Raltegravir | 65 |

[a] Adapted from: Pretorius E, Klinker H, Rosenkranz B. The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. *Ther Drug Monit.* 2011;33(3):265-274.

Several adult and pediatric studies have suggested that TDM can have some utility in assessing adherence, guiding dosing, and predicting efficacy of ARV drugs.[1-13] Despite this evidence, the routine use of TDM in adult and pediatric patients is not recommended for the following reasons: lack of prospective studies that demonstrate improved clinical outcomes, uncertain target ranges for most ARV drugs, high intrapatient and interpatient variability in drug concentrations, and a lack of commercial laboratories that provide real-time quantitation of ARV plasma concentrations.

There are special considerations with dosing of ARV drugs in children living with HIV compared to adults, including dependence on chronologic age and/or body parameters (e.g., height, weight). Ongoing growth requires continuous reassessment of dosing of ARV drugs in order to avoid low drug exposure and development of viral resistance and virologic failure. Developmental differences in drug absorption, distribution, metabolism, and elimination contribute to high variability and a greater frequency of suboptimal exposure to multiple therapeutic agents in children (particularly very young children) compared to adults.[14] Suboptimal exposure to selected ARV drugs has been demonstrated in pediatric patients, especially in young children; therefore TDM may be helpful in the management of pediatric antiretroviral therapy.[7,15-18]

TDM is also useful in children when pharmacogenetics considerations are important in selection of drug dosing. For example, the known effect of the metabolic enzyme CYP2B6 G516T polymorphism on the pharmacokinetics (PK) of efavirenz appears to be most pronounced in younger children undergoing maturation of CYP450 enzymatic system during the first 3 years of life, compared to older children and adults.[18] The significant effect of this polymorphism has prompted dosing guidelines to be based on the patient CYP2B6 G516T genotype of children aged <3 years, along with subsequent confirmation of the efavirenz exposure through TDM (see efavirenz).

Pediatric ARV drug recommendations are often based on extrapolation of efficacy results from large clinical trials in adults, and dosing recommendations for ARV drugs at the time of pediatric drug approval are frequently derived from a limited number of patients and PK modeling, and may be revised as newer PK data become available.[7] While the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend routine TDM for pediatric antiretroviral therapy management, TDM can be considered for certain ARV agents when the approved pediatric formulation and/or dosing are based on limited PK and efficacy data in small populations (see specific drug information sections) or for certain clinical scenarios outlined in the text box above to ensure adequate drug concentrations and/or to decrease toxicity.

## *Practical Considerations*

The accurate interpretation of TDM requires evaluation and documentation of the following:

- The dose and formulation
- Concomitant medications
- Food intake with the dose
- Timing of the dose relative to blood sample collection
- Adherence and resistance information

Additional practical suggestions on TDM of ARV drugs can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee[19] and pediatric TDM manuscripts.[6,20] Most importantly, consultation with an expert in pediatric HIV pharmacology is strongly recommended to obtain guidance on when to obtain samples for TDM, how to interpret the PK data, and how to evaluate the need for dose adjustment and repeat PK evaluation and follow up.

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# Appendix A: Pediatric Antiretroviral Drug Information

## Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

# Abacavir (ABC, Ziagen) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

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

**Tablets:** 300 mg (scored)

**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 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 counts for more than 6 months (24 weeks) on abacavir twice daily, dose can be changed from twice daily to once daily (see text below).

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

| Weight (kg) | Scored 300-mg Tablet | | |
|---|---|---|---|
| | Twice Daily AM Dose | Twice Daily PM Dose | Once Daily Dose |
| 14 to <20 kg | ½ tablet (150 mg) | ½ tablet (150 mg) | 1 tablet (300 mg) |
| ≥20 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).
- 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.

## 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.

- In patients who can be treated with pill formulations, therapy can be initiated with once-daily administration. If therapy was initiated with twice-daily liquid abacavir, then it can be changed from twice daily to once daily in clinically stable patients with undetectable viral load and stable CD4 cell counts (without decline) for more than 6 months (24 weeks) (see text below).

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

- 300 mg twice daily or 600 mg once daily.

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

*Adolescent (Weight ≥40 kg)/Adult Dose:*

- One tablet twice daily.

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

*Adolescent (Weight ≥25 kg) and Adult Dose:*

- One tablet once daily.

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

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

- One tablet once daily.

## Metabolism/Elimination

- Systemically metabolized by alcohol dehydrogenase and glucuronyltransferase.
- Intracellularly metabolized to carbovir triphosphate (CBV-TP).
- 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 (CrCl) <50 mL/min and patients on dialysis (because of the fixed dose of lamivudine).

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- Abacavir does not inhibit, nor is it metabolized by, hepatic cytochrome P (CYP) 450 enzymes. Therefore, it does not cause changes in clearance of agents metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (see more information in Drug Interaction section under Pediatric Use).
- Through interference with alcohol dehydrogenase and glucuronyltransferase, alcohol increases abacavir levels by 41%.

***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 include 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 an 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

### Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

### Pediatric Use

*Approval*

Abacavir is Food and Drug Administration (FDA)-approved for use in children 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.[1-5] Abacavir in combination with lamivudine has been compared to tenofovir disoproxil fumarate with emtricitabine in several adult studies and meta-analyses with variable results.[6-9]

### 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.[10]

*Exposure-Response Relationship*

Plasma area under the drug-concentration-by-time curve (AUC) correlates with virologic efficacy of abacavir, although the association is weak.[11,12] The active form of abacavir is the intracellular metabolite carbovir triphosphate (CBV-TP). Measurement of intracellular CBV-TP is more difficult than measurement of plasma AUC, and changes in plasma AUC may not reflect true changes in intracellular active drug.[13]

*Drug Interactions*

Abacavir plasma 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.[14] In a study comparing PK parameters of abacavir in combination with either LPV/r or nevirapine, abacavir plasma AUC was decreased 40% by concurrent use of LPV/r; however, the CBV-TP concentrations appeared to be increased in the LPV/r cohort.[15] When combined with darunavir/ritonavir, abacavir plasma AUC and trough concentrations were decreased by 27% and 38%, respectively; the CBV-TP AUC and trough concentrations were decreased by 12% and 32%, respectively.[16] The mechanism and the clinical significance of these drug interactions with the PIs are unknown and need to be evaluated. No dose adjustments for abacavir or PIs are currently recommended.

### Dosing

*Appropriate Total Daily Dose*

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 abacavir of 600 mg 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 pill formulation.[17] There is no difference in the abacavir plasma $C_{max}$ and AUC for abacavir oral solution compared to tablet formulations.[18] Doses of liquid abacavir similar to those used for weight band dosing with tablets might be considered in some situations, especially in rapidly growing younger children.

*Frequency of Administration*

New PK data suggest that once-daily dosing of abacavir in children is feasible. 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, but in infants and young children initiating therapy with liquid formulations of abacavir, twice-daily dosing is recommended with consideration of a switch to once-daily dosing after 6 months (24 weeks) when viral load is undetectable and CD4 cell count is stable (without decline). This recommendation is based on the data presented below.

The PK of abacavir dosed once daily in pediatric subjects with HIV-1 infection aged 3 months through 12 years was evaluated in three trials (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).[17,19-22] All three trials were two-period, crossover, open-label PK trials of twice- versus once-daily dosing of abacavir and lamivudine. For the oral solution as well as the tablet formulation, these three trials demonstrated that once-daily dosing provides comparable $AUC_{0-24}$ to twice-daily dosing of abacavir at the same total daily dose. The mean $C_{max}$ was approximately 1.6- to 2.3-fold higher with abacavir once-daily dosing compared with twice-daily dosing.[23]

A pediatric PK model developed based on data from 69 children in the PENTA-13 and PENTA-15 trials and the ARROW study predicted that steady state peak ($C_{max}$) and $AUC_{0-12}$ abacavir concentrations on standard twice-daily dosing were lower in toddlers, and infants aged 0.4 to 2.8 years when compared with children aged 3.6 to 12.8 years. Model-based predictions also showed that equivalent systemic plasma abacavir exposure was achieved after once- or twice-daily dosing regimens in infants, toddlers and children up to age 12 years.[24] The pediatric studies referenced above enrolled only patients who had low viral loads and were clinically stable on twice-daily abacavir before changing to once-daily dosing. Efficacy data from 48-week follow-up in the ARROW trial demonstrated clinical non-inferiority of once-daily (336 children) versus twice-daily abacavir (333 children) in combination with a once- or twice-daily lamivudine-based regimen.[3] No clinical trials have been conducted involving children who initiated therapy with once-daily dosing of abacavir solution.

***Toxicity***

Abacavir has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,[1,2,25] and fewer bone and renal toxicities than tenofovir disoproxil fumarate.[8,26]

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# Didanosine (ddI, Videx) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Videx Pediatric Powder for Oral Solution:** Reconstituted 10 mg/mL

**Videx Enteric-Coated (EC) Delayed-Release Capsules (EC Beadlets):** 125 mg, 200 mg, 250 mg, and 400 mg

**Generic Didanosine Delayed-Release Capsules:** 125 mg, 200 mg, 250 mg, and 400 mg

**Tablets for Oral Suspension:** 100 mg, 150 mg, and 200 mg

## Dosing Recommendations

**Neonatal/Infant Dose (Aged 2 Weeks to <3 Months):**

- 50 mg/m$^2$ of body surface area every 12 hours
- See dosing section below for justification of this dose.

**Infant Dose (Aged ≥3 Months to 8 Months):**

- 100 mg/m$^2$ body surface area every 12 hours

**Pediatric Dose of Oral Solution (Age >8 Months):**

- 120 mg/m$^2$ body surface area every 12 hours
- Dose range: 90–150 mg/m$^2$ body surface area every 12 hours. Do not exceed maximum adult dose; see table below.
- In treatment-naive children ages 3–21 years, 240 mg/m$^2$ body surface area once daily (oral solution or capsules) has effectively resulted in viral suppression.

**Pediatric Dose of Videx EC or Generic Capsules (Aged 6–18 Years and Weighing ≥20 kg)**

| Body Weight (kg) | Dose (mg) |
|---|---|
| 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 (kg) | Dose (mg) |
|---|---|
| <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 TDF 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 and tablets for oral suspension contain 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.
- If using tablets for oral suspension: Tablets are not to be swallowed whole. For full

**Pediatric/Adolescent Dose of Didanosine when Combined with Tenofovir Disoproxil Fumarate (TDF):**

- This combination should be avoided because of enhanced didanosine toxicity, reports of immunologic non-response, high rates of early virologic failure and rapid selection of resistance mutations (Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents).

therapeutic effect, 2 tablets may be chewed or dispersed in water before administration. To disperse tablets: add 2 tablets to at least 1 ounce (30 mL) of water. Drink entire dispersion immediately. For children 1 or 2 tablets may be chewed or dispersed in water before administration.

## Metabolism/Elimination

- Renal excretion 50%
- 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Absorption:* Antacids in didanosine oral solution and tablets for oral 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) and 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. That combination should be avoided (see 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 with didanosine 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 and retinal depigmentation and optic neuritis have been reported. Fall in CD4 T lymphocyte count is reported with use of didanosine with TDF.
- *Rare:* Non-cirrhotic portal hypertension, presenting clinically with hematemesis, esophageal varices, ascites, and splenomegaly, and associated with increased transaminases, increased alkaline phosphatase, and thrombocytopenia, has been associated with long-term didanosine use.[1]
- *Possible risk of cancer after in-utero exposure:* In a study of 15,163 children without HIV infection who were exposed to at least 1 NRTI *in utero*, 21 cancers were identified. Didanosine accounted for only 10% of prescriptions but was associated with one-third of cancers, and, in multivariate analysis, was associated with a 5.5-fold (95% C, 2.1–14.4) increased risk with first-trimester exposure. 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.standford.edu/DR/).

***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 due to its significant toxicity and the availability of safer agents.

***Dosing***

*Standard Dose in Children Aged >8 months*

The standard dose of didanosine oral solution in children aged >8 months is 120 mg/m$^2$ body surface area twice daily.[2,3] Doses higher than 180 mg/m$^2$ body surface area twice daily are associated with increased toxicity.[4]

*Special Considerations in Ages 2 Weeks to <8 Months*

For infants aged 2 weeks to 8 months, the FDA recommends 100 mg/m$^2$ 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 concern for increased toxicity in this younger age group, the Panel recommends a dose of 50 mg/m$^2$ of body surface area twice daily for infants aged 2 weeks to 3 months, with an increase to 100 mg/m$^2$/dose twice daily at 3 months, and finally increasing to 120 mg/m$^2$ body surface area per dose twice daily at age 8 months (as above).

*Frequency of Administration (Once-Daily or Twice-Daily)*

In those older than 3 years of age, a once-daily dosing regimen may be preferable to promote adherence, and multiple studies support the favorable PKs and efficacy of once-daily dosing of 240 mg/m$^2$ body surface area.[5]

*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.[6] 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.[7,8] A European study dosed didanosine oral solution as part of a 4-drug regimen either 1 hour before or 1 hour after meals, but allowed the extended-release formulation to be given without food restriction and showed good virologic outcome with up to 96 weeks of follow-up.[9]

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# Emtricitabine (FTC, Emtriva) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Pediatric Oral Solution:** 10 mg/mL

**Capsules:** 200 mg

**Generic Formulations:** None available

**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
- *[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

## Dosing Recommendations

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

*Oral Solution:*

- 3 mg/kg once daily.

**Note:** Please see Special Considerations for Neonates section.

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

*Oral Solution:*

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

*Capsules (Weight >33 kg):*

- 200 mg once daily.

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

*Oral Solution for Those Unable to Swallow Capsules:*

- 240 mg (24 mL) once daily.

*Capsules:*

- 200 mg once daily.

### Combination Tablets

*[Truvada tablet] Emtricitabine plus TDF*

## Selected Adverse Events

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

## Special Instructions

- Although emtricitabine can be administered without regard to food, food requirements vary depending on the other ARV drugs contained in a combination tablet. For Atripla (administer without food) and Complera (administer with a meal of at least 500 calories), refer to efavirenz or rilpivirine special instructions.
- 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.
- If using Stribild, please see the elvitegravir section of the drug appendix for additional information.
- Before using emtricitabine, screen patients for HBV.

## Metabolism/Elimination

- Limited metabolism: No cytochrome P (CYP) 450 interactions.

**Truvada Tablets Dosing Table**

| **Body Weight** kg | **FTC/TDF Tablet** Once Daily |
|---|---|
| 17 to <22 | One 100 mg/150 mg tablet |
| 22 to <28 | One 133 mg/200 mg tablet |
| 28 to <35 | One 167 mg/250 mg tablet |
| Adolescent (Weighing ≥35 kg) and Adult Dose | One 200 mg/300 mg tablet |

*[Descovy] Emtricitabine plus TAF*

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

- 1 tablet once daily

*[Atripla] Efavirenz plus Emtricitabine plus TDF 300 mg*

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

- 1 tablet once daily.
- Administer without food.
- See efavirenz section for pregnancy warning.

*[Complera] Emtricitabine plus Rilpivirine plus TDF*

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

- 1 tablet once daily in treatment-naive patients with baseline plasma RNA <100,000 copies/mL or virologically suppressed patients with no history of virologic failure, resistance to rilpivirine and other antiretroviral (ARV) drugs, and who are currently on their first or second regimen.
- Administer with a meal of at least 500 calories.

*[Odefsey] Emtricitabine plus Rilpivirine plus (TAF)*

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

- 1 tablet once daily with a meal as initial therapy in those with no antiretroviral treatment (ART) history with HIV-1 RNA ≤100,000 copies per mL; or to replace a stable ART regimen in those who are 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*

**Adult Dose (Aged ≥18 Years):**

- 1 tablet once daily in treatment-naive or virologically suppressed adults.
- Administer with a meal.

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

- Renal excretion 86%: Potential competition with other compounds that undergo renal elimination.
- Dosing of emtricitabine in patients with renal impairment: Decrease dosage in patients with impaired renal function. Consult manufacturer's prescribing information.
- Do not use Atripla (fixed-dose combination) in patients with creatinine clearance (CrCl) <50 mL/min or in patients requiring dialysis.
- Do not use Truvada (fixed-dose combination) in patients with CrCl <30 mL/min or in patients requiring 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 be increased 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 in patients with estimated CrCl below 30 mL per minute.

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

- 1 tablet once daily with food in ART-naive patients or to replace the current ART 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.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

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

***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/hepatitis B (HBV) coinfection 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***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 combination 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 (e.g., tenofovir or abacavir versus the more static components like emtricitibine or lamivudine). Emtricitabine and lamivudine have been considered interchangeable, but little data exist to make this recommendation in antiretroviral (ARV)-naive patients. Investigators in the ATHENA cohort compared naive patients who started tenofovir plus emtricitabine or tenofovir plus lamivudine in combination with a ritonavir-boosted protease inhibitor (darunavir, atazanavir, or lopinavir).[1] The adjusted hazard ratio for virologic failure of lamivudine compared to emtricitabine 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 the time to virologic failure after attaining suppression. Yang et al. in the Swiss cohort found a potential difference in efficacy which disappeared after adjusting for pill burden.[2] Current evidence suggests that emtricitabine and lamivudine have equivalent efficacy and toxicity in ARV-naive patients.

*Efficacy*

Based on a dose-finding study described below,[3] emtricitabine was studied at a dose of 6 mg/kg once daily in combination with other ARV drugs in 116 patients aged 3 months to 16 years.[4,5] PK results were similar, and follow-up data extending to Week 96 indicated that 89% of the ARV-naive and 76% of the ARV-experienced children maintained suppression of plasma HIV RNA <400 copies/mL (75% of ARV-naive children and 67% of ARV-experienced children at <50 copies/mL). Minimal toxicity was observed in this trial. The Saez-Lorens study used a maximum of 240 mg of the liquid formulation. In PACTG P1021,[4] emtricitabine at a dose of 6 mg/kg (maximum 200 mg/day as liquid) in combination with didanosine and efavirenz, all given once daily, was studied in 37 ARV-naive children with HIV aged 3 months to 21 years. Eighty-five percent of children achieved HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 T lymphocyte count rose by 329 cells/mm$^3$ at Week 96.

*Pharmacokinetics Liquid Versus Capsule*

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

*Pharmacokinetics in Infants*

A study in South Africa evaluated the PKs of emtricitabine in 20 infants with perinatal HIV exposure aged <3 months, given emtricitabine as 3 mg/kg once daily for two, 4-day courses, separated by an interval of ≥2 weeks.[6] Emtricitabine exposure (area under the curve [AUC]) in neonates receiving 3 mg/kg emtricitabine once daily was in the range of pediatric patients aged >3 months receiving the recommended emtricitabine dose of 6 mg/kg once daily and adults receiving the once-daily recommended 200-mg emtricitabine dose (AUC approximately 10 hr* µg/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.[7] Extensive safety data are lacking in this age range.

*Considerations for Use*

Formulations favor liquid emtricitabine over liquid lamivudine, since the 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, again lamivudine and emtricitabine are equivalent.

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

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# Lamivudine (3TC, Epivir) (Last updated April 27, 2017; last reviewed April 27, 2017)

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[a])

**Tablets:** 150 mg (scored) and 300 mg (generic); 100 mg (Epivir HBV[a])

**Fixed-Dose Combination Tablets:**

- [*Combivir and generic*] Lamivudine 150 mg plus zidovudine 300 mg
- [*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

**Tablets:** 100 mg, 150 mg, and 300 mg

## Dosing Recommendations

### Neonate and Infant Dose (Birth to <4 Weeks):

- 2 mg/kg twice daily

**Note:** Please see Infant ARV Prophylaxis in the Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States for dosing used to prevent perinatal transmission.

### Pediatric Dose (Aged ≥4 Weeks):

- 4 mg/kg (up to 150 mg) twice daily
- In infants and young children being treated with liquid formulations of lamivudine, initiation with once-daily lamivudine is not generally recommended. Please refer to text for more detail.

**Weight-Band Dosing (Weighing ≥14 kg)**
***Scored 150 mg tablet***

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

## Selected Adverse Events

- Minimal toxicity
- 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.

## Metabolism/Elimination

- Renal excretion: Dosage adjustment required in renal insufficiency.
- Fixed-dose combination tablets should not be used in patients with creatinine clearance <50 mL/min, on dialysis, or with impaired hepatic function.

**Note:** The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged **≥3 years** with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 T lymphocyte count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily.

**Adolescent and Adult Dose:**
*Weighing <25 kg:*

- 4 mg/kg (up to 150 mg) twice daily

*Weighing ≥25 kg:*

- 150 mg twice daily or 300 mg once daily

**[*Combivir and Generic*] Lamivudine/Zidovudine**
*Adolescent (Weighing ≥30 kg)/Adult Dose:*

- 1 tablet twice daily

**[*Trizivir and Generic*] Abacavir/Lamivudine/Zidovudine**
*Adolescent (Weighing ≥40 kg)/Adult Dose:*

- 1 tablet twice daily

**[*Epzicom*] Abacavir/Lamivudine**
Adolescent (Weighing ≥25 kg)/Adult Dose:

- 1 tablet once daily

**[*Triumeq*] Abacavir/Dolutegravir/Lamivudine**
*Adolescent (Weighing ≥40 kg)/Adult Dose:*

- 1 tablet once daily

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

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Renal elimination:* Drugs that decrease renal function could decrease clearance of lamivudine.
- *Other nucleoside reverse transcriptase inhibitors:* Do not use lamivudine in combination with emtricitabine because of the similar resistance profiles and no additive benefit.[1] Do not use separately when prescribing Truvada, Atripla, Complera, or Stribild because emtricitabine is a component of these formulations. Do not use separately when prescribing Combivir, Epzicom, 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

Lamivudine is Food and Drug Administration (FDA)-approved for the treatment of children aged ≥3 months; it is a common component of most nucleoside backbone regimens.

*Considerations for Use*

The efficacy and toxicity of lamivudine are equivalent to emtricitabine. 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, again, 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 or abacavir versus the more static components [e.g. emtricitabine or lamivudine]). Emtricitabine and lamivudine have been considered interchangeable, but little data exists to make this recommendation in ARV-naive patients. Investigators in the ATHENA cohort compared naive patients who started tenofovir/emtricitabine or tenofovir/lamivudine in combination with a boosted protease inhibitor (darunavir, atazanavir, or lopinavir).[2] The adjusted hazard ratio for virologic failure of lamivudine compared to emtricitabine 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 the time to virologic failure after attaining suppression. Yang et al. in the Swiss cohort found a potential difference in efficacy which disappeared after adjusting for pill burden. Current evidence suggests that emtricitabine and lamivudine are equivalent even in ARV-naive patients.[3]

*Efficacy*

Lamivudine has been studied in children with HIV alone and in combination with other ARV drugs. Extensive data demonstrate that lamivudine appears safe and is associated with clinical improvement and virologic response, and it is commonly used in children with HIV as a component of a dual-nucleoside reverse transcriptase inhibitor (NRTI) backbone.[4-12] In 1 study, the NRTI background components of lamivudine/abacavir were superior to zidovudine/lamivudine or zidovudine/abacavir in long-term virologic efficacy.[13]

*Pharmacokinetics in Infants*

Because of its safety profile and availability in a liquid formulation, lamivudine has been given to infants during the first 6 weeks of life starting at a dose of 2 mg/kg every 12 hours before age 4 weeks.[9] A population pharmacokinetic (PK) analysis of infants receiving lamivudine affirms that adjusting the dose 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.[14] For infants in early life, the higher World Health Organization weight-band dosing (up to 5 times the FDA dose) results in increased plasma concentrations compared to the 2 mg/kg dosing.[15] In HPTN 040, lamivudine was given for prophylaxis of perinatal transmission in 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 6 mg twice daily and infants weighing ≤2,000 g received 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.[16]

*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 approximately 25% lower plasma concentrations of lamivudine compared with 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. The relative bioavailability of lamivudine oral solution is approximately 40% lower than tablets containing lamivudine in pediatric subjects despite no difference in adults. The mechanisms for the diminished relative bioavailability of lamivudine solution are unknown,[17] but a recent study in adults comparing the PK of lamivudine solution either alone or with increasing concentrations of sorbitol indicates that sorbitol decreases the total exposure of lamivudine solution.[18] Sorbitol is a component of several ARV solutions used in pediatric patients, and this may explain the PK discrepancy between oral solution and tablet formulations. There are currently no studies supporting an increase in dosing for lamivudine oral solution in children.

*Dosing Considerations—Once-Daily versus Twice-Daily Administration*

The standard adult dosage 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 8 mg/kg leads to area under the curve $(AUC)_{0\text{-}24}$ values similar to 4 mg/kg twice daily but $C_{min}$ values significantly lower and $C_{max}$ values significantly higher in children ages 1 to 18 years.[19] Intensive PKs of once-daily versus twice-daily dosing of lamivudine were evaluated in children with HIV aged 2 to 13 years in the PENTA-13 trial,[4] and in children aged 3 to 36 months in the PENTA 15 trial.[20] Both trials were crossover design with doses of lamivudine of 8 mg/kg/once daily or 4 mg/kg/twice daily. $AUC_{0\text{-}24}$ and clearance values were similar and most children maintained an undetectable plasma RNA value after the switch. A study of 41 children aged 3 to 12 years (median age 7.6 years) in Uganda who were stable on twice-daily lamivudine also showed equivalent $AUC_{0\text{-}24}$ 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.[21] All 3 studies enrolled only patients who had low viral load or were clinically stable on twice-daily lamivudine before changing to once-daily dosing. Nacro et al. studied a once-daily regimen in ARV-naive children in Burkina-Faso composed of non-enteric-coated (EC) didanosine, lamivudine, and efavirenz. Fifty-one children ranging in age from 30 months to 15 years were enrolled in this open-label, Phase II study lasting 12 months.[22] The patients had advanced HIV with a mean CD4 percentage of 9 and median plasma RNA of 5.51 log10/copies/mL. At 12-month follow-up, 50% of patients had a plasma RNA <50 copies/mL and 80% were <300 copies/mL with marked improvements in CD4 percentage. Twenty-two percent of patients harbored multi-class-resistant viral strains. While PK values were similar to the PENTA and ARROW trials, the study was complicated by use of non-EC didanosine, severe immunosuppression, and non-clade B virus. In addition, rates of virologic failure and resistance profiles were not separated by age. Therefore, the Panel supports consideration of switching to once-daily dosing of lamivudine from twice-daily dosing in clinically stable patients aged ≥3 years with a reasonable once-daily regimen, an undetectable viral load, and stable CD4 cell count, at a dose of 8 to 10 mg/kg/dose to a maximum of 300 mg once daily. 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 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 have been shown to be equivalent with once- and twice-daily dosing in adults and adolescents, supporting a recommendation for once-daily lamivudine dosing based upon FDA recommendations or drug co-formulations.[23,24]

*World Health Organization Dosing*

Weight-band dosing recommendations for lamivudine have been developed for children weighing at least 14 kg and receiving the 150-mg scored tablets.[25,26]

Both emtricitabine and lamivudine have antiviral activity and efficacy against HBV. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, please see the [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children](#).

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# Stavudine (d4T, Zerit) (Last updated April 27, 2017; last reviewed April 27, 2017)

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, 40 mg

## Dosing Recommendations

### Neonate/Infant Dose (Birth to 13 Days):

- 0.5 mg/kg per dose twice daily

### Pediatric Dose (Aged ≥14 Days and Weighing <30 kg):

- 1 mg/kg per dose twice daily

### Adolescent (≥30 kg)/Adult Dose:

- 30 mg per dose twice daily

## Selected Adverse Events

- Mitochondrial toxicity, highest risk of all NRTI drugs
- Peripheral neuropathy is dose-related and occurs more frequently in patients with advanced HIV disease, a 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 nucleoside reverse transcriptase inhibitors). The risk is increased when 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 [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents] and [http://www.hiv-druginteractions.org/])

- *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 are more often reported 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 receiving combination 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 and occurs more frequently in patients with advanced HIV disease, a 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. The combination of stavudine with 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 for initial therapy. Risk factors found to be associated with lactic acidosis in adults include female gender, obesity, and prolonged nucleoside exposure.[1]
- *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. Non-cirrhotic portal hypertension with prolonged exposure.

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10), and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

Although stavudine is Food and Drug Administration (FDA)-approved for use in infants and children, it is not recommended for use by the Panel 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 alone or in combination with other antiretroviral (ARV) agents demonstrate that stavudine is associated with clinical and virologic response.[2-8] In resource-limited countries, stavudine is frequently a component of initial ART with lamivudine and nevirapine in children, often as a component of fixed-dose combinations not available in the United States. In this setting, reported outcomes from observational studies are good; data show substantial increases in the CD4 T lymphocyte (CD4) cell count and complete viral suppression in 50% to 80% of treatment-naive children.[9-12] 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 TMP-SMX prophylaxis.[13] Short-term use of stavudine in certain settings where access to other ARVs may be limited remains an important strategy for treatment of children.[14,15]

### *Toxicity*

Stavudine is associated with a higher rate of adverse events than zidovudine in adults and children receiving ART.[16,17] 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 those containing zidovudine, with pancreatitis, peripheral neuropathy, and lipodystrophy/lipoatrophy (fat maldistribution) associated more often with stavudine use.[17] Peripheral neuropathy is an important toxicity associated with stavudine but appears to be less common in children than in adults.[3,18]

#### *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.[19-22] Children with metabolic disorders and abnormalities in body fat distribution, including fat loss and central fat accumulation, may be at increased risk of cardiovascular disease in early adulthood.[23,24] Stavudine use has consistently been associated with a higher risk of lipodystrophy and other metabolic abnormalities (e.g., insulin resistance) in multiple pediatric studies involving children.[23-30] Lipodystrophy developed in 27% to 66% of children, with lipoatrophy being the most common form of lipodystrophy. While ever- or current-stavudine use has consistently been associated with a higher risk of LS, additional factors include older age and duration on ARVs.[26,27] Improvements in (or resolution of) lipodystrophy were reported in 22.9% to 73% of cases after discontinuation of stavudine in two separate studies.[28,31]

Lactic acidosis with hepatic steatosis, including fatal cases, has been reported with use of nucleoside analogues, including stavudine, alone or in combination with didanosine.[32-34]

#### *Mechanism*

Many of the above-mentioned 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.[32,35-37] In a recent analysis involving a large cohort of pediatric patients (PACTG protocols 219 and 219C), possible mitochondrial dysfunction was associated with NRTI use, especially in children receiving stavudine and/or lamivudine.[38]

#### *World Health Organization Recommendations*

The World Health Organization (WHO) strongly recommends that a maximum stavudine dose of 30 mg twice daily be used instead of the FDA-recommended 40 mg twice daily in patients weighing 60 kg or more.[39,40] Studies comparing the efficacy and toxicity of the two doses have consistently shown that the 30-mg dose is associated with similar efficacy and lower toxicity than the 40-mg dose but the overall incidence of toxicity is considered to be unacceptably high.[41-45] WHO recommends that stavudine be phased out of use in all patients because of concerns about unacceptable toxicity, even at the lower dose, since safer alternative agents can be prescribed.

### *Pharmacokinetics*

Current pediatric dosing recommendations are based on early pharmacokinetic (PK) studies designed to achieve exposure (area under the curve) in children similar to that found in adults receiving a dose with proven efficacy.[46] Although WHO has recommended a reduced dose in adults, a similar dose reduction has not been suggested in children. A reduced pediatric dose has been proposed based on PK modeling, but clinical data on intracellular concentrations of the active stavudine triphosphate are lacking.[47,48]

### *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 is equivalent with stavudine administered in an intact or a dispersed capsule, dosing with the dispersal method can be used as an alternative to the oral solution.[49]

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# Tenofovir Alafenamide (TAF, Genvoya) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**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

## Dosing Recommendations

### Combination Tablets

*[Descovy] Emtricitabine 200 mg plus TAF 25 mg*

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

- 1 tablet once daily

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

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

- 1 tablet once daily with food in antiretroviral (ARV) treatment-naive patients or to replace the current ARV regimen in those who are virologically suppressed (i.e., HIV-1 RNA <50 copies/mL) and 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 ≥35 kg) and Adult Dose:**

- 1 tablet once daily with a meal as initial therapy in those with no ARV treatment history with HIV-1 RNA less than or equal to 100,000 copies per mL; or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 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.

## 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 use of 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.
- If using Descovy please see the Emtricitabine section of the drug appendix.
- If using Genvoya please see the Elvitegravir, Emtricitabine, and Cobicistat sections of the drug appendix for additional information.
- Use of Genvoya is not recommended with other ARV drugs.
- Do not use Genvoya with elvitegravir, cobicistat, tenofovir disoproxil fumarate, emtricitabine, lamivudine, or protease inhibitors co-formulated with cobicistat.
- When using Odefsey, refer to the Emtricitabine and Rilpivirine sections of the drug appendix. 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).

## Pharmacology

- TAF undergoes renal excretion.
- Dosing in patients with renal insufficiency: TAF-containing formulations are not recommended in patients with estimated creatinine clearance below 30 mL per minute.

- TAF-containing formulations do not require dosage 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.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- *Metabolism:* Genvoya contains elvitegravir and cobicistat. 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-glycoprotein and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists for multiple drug interactions when using both elvitegravir and cobicistat.
- Odefsey contains rilpivirine which is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before Genvoya or Odefsey 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 tenofovir alafenamide (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):* 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 (see https://www.iasusa.org/sites/default/files/tam/22-3-642.pdf) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

TAF is Food and Drug Administration (FDA)-approved for use in children aged at least 12 years and weighing at least 35 kg when used as part of the single-tablet regimen of elvitegravir/cobicistat/emtricitabine/TAF (EVG/COBI/FTC/TAF), or when used as the co-formulated TAF/FTC as part of an antiretroviral therapy regimen. While TAF/FTC/rilpivirine (RPV) is not FDA-approved for use in persons aged <18 years, each componenet of the regimen is approved for use in children aged at least 12 years and weighing at least 35 kg. 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 (reviewed in Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Children).

***Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate***

Both tenofovir disoproxil fumarate (TDF) and TAF are prodrugs of the nucleotide reverse transcriptase tenofovir (TFV). After oral administration TDF is well absorbed,[1,2] 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).[3] TFV is the main compound measurable in plasma after TDF administration. From the bloodstream TFV enters cells and is phosphorylated to the active agent tenofovir diphosphate (TFV-DP).

TAF[4] also has good oral bioavailability.[5] 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 compared to TDF, and the main component in plasma is the prodrug itself, TAF.[6] Once inside the cell, TAF is hydrolyzed to TFV,[7,8] 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.[4] Therefore a lower dose of TAF results in equivalent or higher concentrations of TFV-DP inside cells compared to the much higher doses of TDF needed to attain a similar intracellular TFV-DP concentration.

The key pharmacokinetic difference between TDF and TAF is that TDF results in higher plasma TFV concentration compared to TAF, but when administered at FDA-approved doses, both result in equivalent intracellular TFV-DP concentrations.[6] 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 associated with TDF-related endocrine disruption that is associated with low bone mineral density (BMD)[9] and with both glomerular[9,10] and proximal tubular[11] toxicity. If some of the TDF-associated nephrotoxicity is from intracellular damage to mitochondria,[12] studies of longer duration may be needed to confirm the renal tubular safety of TAF.

**Table 1: Multiple-Dose Pharmacokinetics at Day 10 of Once-Daily Oral Administration in Adults with HIV Infection[a]: TAF vs. TDF.[6]**

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

[a] Mean age 38 years; range 20–57 years

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

**Key to Acronyms:** AUC = area under the curve; PBMC = peripheral blood mononuclear cell; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

### *Tenofovir Alafenamide Efficacy in Clinical Trials in Adults and Adolescents*

In adults, TAF is non-inferior to TDF over 48 weeks in its ability to control viral load in combination with elvitegravir, cobicistat, and emtricitabine,[13-15] with darunavir/cobicistat/emtricitabine,[16] and when TAF-emtricitabine is administered in combination with other antiretroviral drugs.[17] TAF shows similar efficacy in children aged at least 12 years and weighing at least 35 kg.[18]

### *Pharmacokinetics*

*Relationship of Drug Exposure to Virologic Response*

Virologic success is most closely related to intracellular TFV-DP concentrations. There are no data available for intracellular TFV-DP in children or adolescents treated with TAF, but the peripheral blood mononuclear cell TFV-DP concentration in adults is similar with TDF and TAF.[6,13] In 24 pediatric patients aged 12 to <18 years who received EVG/COBI/FTC/TAF the plasma TAF area under the curve was decreased 23% compared to exposures achieved in treatment-naive adults. The clinical significance of this is unclear.[19]

### *Formulations*

TAF is available as the co-formulated tablets FTC/TAF,[20] EVG/COBI/FTC/TAF,[19] and FTC/TAF/RPV.[21] The amount of TAF (10 mg) in EVG/COBI/FTC/TAF is lower than the amount of TAF (25 mg) in FTC/TAF or FTC/TAF/RPV because cobicistat boosts TAF blood concentrations. TAF-containing pills are smaller than their TDF-containing counterparts, a significant advantage for some pediatric patients who may have trouble swallowing larger pills.

### *Toxicity*

*Bone*

TAF less frequently causes bone toxicity compared to TDF.[13-17] 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 spine (mean change –1·30% vs. –2·86%; $P < 0.0001$) and hip (–0·66% vs. –2·95%; $P < 0.0001$) at 48 weeks compared to those given EVG/COBI/FTC/TDF.[13] These differences were maintained to 96 weeks.[22]

*Renal*

Short-term studies in adolescents age 12 to 17 years[18] and 48-week studies in adults[13-17] show that TAF less frequently is associated with glomerular and renal tubular damage than is TDF. For example, in one study of 1733 randomized adult participants with HIV, those treated with EVG/COBI/FTC/TAF had smaller mean increase in serum creatinine (0.08 vs. 0·12 mg/dL; $P < 0.0001$) compared to those given EVG/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[13], and these differences persisted to 96 weeks of follow-up.[22] Safety of EVG/COBI/FTC/TAF has been shown in adults with estimated creatinine clearance between 30 and 69 mL/min.[23] For TAF, less intense renal safety monitoring may be needed than with TDF, but more experience with the drug in broad clinical practice will be needed before a specific recommendation can be made.

*Lipids*

In treatment-naive adults evaluated after 48 weeks of therapy, the initiation of EVG/COBI/FTC/TAF is associated with increases in serum lipids greater than those observed with the initiation of EVG/COBI/FTC/TDF, with mean increase in total cholesterol of 31 mg/dL versus 23 mg/dL and low-density lipoprotein (LDL) cholesterol of 16 mg/dL versus 4 mg/dL, respectively. In 48 adolescents treated with EVG/COBI/FTC/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.[24] Monitoring serum lipids while the patient is taking EVG/COBI/FTC/TAF seems reasonable given these data.

*Use of Tenofovir Alafenamide in Genvoya in Children Aged 6 to <12 years*

Studies are ongoing of Genvoya in children aged 6 to < 12 years and body weight ≥25 kg.[25]

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# Tenofovir Disoproxil Fumarate (TDF, Viread) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 = 1 g oral powder; supplied with dosing scoop)

**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

## Dosing Recommendations

### Neonate/Infant Dose:

- Not Food and Drug Administration-approved or recommended for use in neonates/infants aged <2 years.

### Pediatric Dose (Aged ≥2 Years to <12 Years)[a]:

- 8 mg/kg/dose once daily

**TDF Oral Powder Dosing Table**

| **Body Weight** kg | **TDF Oral Powder** Once Daily Scoops of Powder |
|---|---|
| 10 to <12 | 2 scoops (80 mg) |
| 12 to <14 | 2.5 scoops (100 mg) |
| 14 to <17 | 3 scoops (120 mg) |
| 17 to <19 | 3.5 scoops (140 mg) |
| 19 to <22 | 4 scoops (160 mg) |
| 22 to <24 | 4.5 scoops (180 mg) |
| 24 to <27 | 5 scoops (200 mg) |
| 27 to <29 | 5.5 scoops (220 mg) |
| 29 to <32 | 6 scoops (240 mg) |
| 32 to <34 | 6.5 scoops (260 mg) |
| 34 to <35 | 7 scoops (280 mg) |
| ≥35 | 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[a]

## 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 antiretroviral (ARV) drugs contained in a combination tablet.

**TDF Tablet Dosing Table**
**(Aged ≥2 Years and Weighing ≥17 kg)**

| **Body Weight** kg | **TDF Tablet** Once Daily |
|---|---|
| 17 to <22 | 150 mg |
| 22 to <28 | 200 mg |
| 28 to <35 | 250 mg |
| ≥35 | 300 mg |

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

- TDF 300 mg once daily

**Combination Tablets**

*[Truvada] Emtricitabine plus TDF*

**Truvada Tablets Dosing Table**

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

*[Atripla] Efavirenz plus Emtricitabine plus TDF*

**Adolescent (Aged ≥12 years and Weighing ≥40 kg) and Adult Dose:**

- 1 tablet once daily.

*[Complera] Emtricitabine plus Rilpivirine plus TDF*

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

- 1 tablet once daily in treatment-naive adults with baseline viral load <100,000 copies/mL or virologically suppressed adults, with no history of virologic failure, resistance to rilpivirine and other ARV drugs, and who are currently on their first or second regimen.
- Administer with a meal of at least 400 calories.

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

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

- 1 tablet once daily in treatment-naive adults or to replace the current ARV regimen in those who are 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 Stribild.
- Administer with food.

For Atripla (administer without food) and Complera (administer with a meal of at least 400 calories), refer to efavirenz or rilpivirine special instructions, respectively.

- 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 13i) during continued therapy. Measure serum phosphate if clinical suspicion of hypophosphatemia.
- Screen patients for hepatitis B virus (HBV) infection before use of TDF. Severe acute exacerbation of HBV infection can occur when TDF is discontinued; therefore, in patients with HBV infection, monitor hepatic function for several months after therapy with TDF is stopped.
- If using Stribild, please see the elvitegravir and cobicistat sections of the drug appendix for additional information.

## Metabolism/Elimination

- Renal excretion
- Dosing of TDF in patients with renal insufficiency: Decreased dosage should be used in patients with impaired renal function (creatinine clearance <50 mL/min). Consult manufacturer's prescribing information for adjustment of dosage in accordance with creatinine clearance (CrCl).
- Atripla and Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Truvada (fixed-dose combination) should not be used in patients with CrCl <30 mL/min or in patients requiring dialysis.
- Stribild should not be initiated in patients with estimated CrCl <70 mL/min and should be discontinued in patients with estimated CrCl <50 mL/min.
- Stribild should not be used in patients with severe hepatic impairment.

[a] See text for concerns about decreased BMD, especially in pre-pubertal patients and those in early puberty (Tanner Stages 1 and 2).

***Drug Interactions*** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents] and [http://www.hiv-druginteractions.org/])

- *Renal elimination:* Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of plasma tenofovir disoproxil fumarate (TDF).
- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Didanosine serum concentrations are increased when the drug is co-administered with TDF and this combination should be avoided if possible because of increase in didanosine toxicity.
- *Protease inhibitors:* TDF decreases atazanavir plasma concentrations. Atazanavir without ritonavir should not be co-administered with TDF. In addition, atazanavir and lopinavir/ritonavir increase plasma tenofovir concentrations and could potentiate TDF-associated toxicity.
- *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; the clinical significance of these changes is not yet known. Renal toxicity, including increased serum creatinine, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed. Patients at increased risk of renal glomerular or tubular dysfunction should be closely monitored. 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

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

TDF has antiviral activity and efficacy against hepatitis B virus (HBV) and is FDA-approved for HBV treatment for children aged 12 years and older (reviewed in Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Children).

***Efficacy in Clinical Trials in Adults Compared to Children and Adolescents***

The standard adult dose of TDF approved by the FDA for adults and children aged ≥12 years and weight ≥35 kg is 300 mg once daily; for children aged 2 to 12 years, the FDA-approved TDF dose is 8 mg/kg/dose administered once daily, which closely approximates the dose of 208 $mg/m^2$/dose used in early studies in children.[1]

In adults, the recommended TDF dose is highly effective. In comparative clinical trials in adults, TDF when used with lamivudine or emtricitabine as a dual-NRTI backbone in combination with efavirenz was superior to zidovudine used with lamivudine and efavirenz in viral efficacy.[2-4] TDF with emtricitabine has been compared to abacavir in combination with lamivudine in several adult studies and meta-analyses with variable results.[5-9]

In children, the published efficacy data are mixed, but potency equal to that in adults is seen in pediatric patients aged 3 to 18 years with susceptible virus. In children aged 2 to <12 years, TDF 8 mg/kg/dose once daily showed non-inferiority to twice-daily zidovudine- or stavudine-containing ART over 48 weeks of randomized treatment.[10,11] Virologic success is lower in treatment-experienced patients with extensive drug resistance.[12-14]

### Pharmacokinetics

*Relationship of Drug Exposure to Virologic Response*

Virologic success is most closely related to intracellular tenofovir diphosphate (TFV-DP) concentrations, and for TDF, intracellular TFV-DP is linked to plasma TFV concentration.[15] A modeling study suggests that children and adolescents treated with TDF may have higher intracellular TFV-DP concentrations than adults[16] even though plasma TFV concentrations are lower in children and adolescents because renal clearance of TFV is higher in children than in adults.[1,17,18]

### 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 in the vehicle, TDF should be administered promptly because, if allowed to sit too long, its taste becomes bitter.

### Toxicity

*Bone*

TDF administration is associated with decreased BMD in both adults[19,20] and children.[11,21-23] When treated with TDF, younger children in Tanner Stages 1 and 2 may be at higher risk of decreased BMD than children with more advanced pubertal development (i.e., Tanner Stage ≥3).[17] Discontinuation of TDF results in partial or complete recovery of BMD.[21]

In the industry-sponsored study that led to FDA approval of TDF in adolescents aged ≥12 years and weight ≥35 kg, 6 of 33 participants (18%) in the TDF arm experienced a >4% decline in absolute lumbar spine BMD in 48 weeks compared with 1 of 33 participants (3%) in the placebo arm.[12]

TDF administration disrupts vitamin D metabolism[24] 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.[25] During chronic TDF administration, in youth with HIV, supplementation with vitamin D3 (50,000 IU once monthly) was associated with decrease in serum parathyroid hormone;[26] the effect on BMD of vitamin D supplementation during chronic TDF administration is under study (ClinicalTrials.gov identifier NCT01751646).

*Monitoring Potential Bone Toxicity*

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., Tanner Stages 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 possibly tenofovir alafenamide) in children in Tanner Stages 1–3, because children with perinatally acquired HIV are at risk for low peak bone mass.[27,28]

*Renal*

New onset or worsening of renal impairment has been reported in adults[29] and children[30,31] receiving TDF, with renal toxicity leading to discontinuation of TDF reported in 3.7% (6 of 159) of children with HIV treated with TDF.[14] While TDF is clearly associated with a decline in glomerular filtration rate, the effect is generally small, and severe glomerular toxicity is rare.[29,30] Irreversible renal failure is quite rare but has been reported.[32]

The main target of TDF nephrotoxicity is the renal proximal tubule.[30] Case reports highlight the infrequent but most severe manifestations of renal Fanconi syndrome, hypophosphatemia, hypocalcemia, diabetes insipidus, myalgias, bone pain, and fractures.[33,34]

Subclinical renal tubular damage is more frequent. Increased urinary beta-2 microglobulin was identified in 27% (12 of 44) of children treated with TDF compared with 4% (2 of 48) of children not treated with TDF.[35] TDF-associated proteinuria or chronic kidney disease is more common with longer duration of treatment.[36,37] Of 89 participants aged 2 to 12 years who received TDF in Gilead study 352 (median drug exposure 104 weeks), 4 were discontinued from the study for renal tubular dysfunction, with the discontinuations occurring between 84 and 156 weeks on TDF therapy.[10]

*Monitoring Potential Renal Toxicity*

Because of the potential for TDF to decrease creatinine clearance and to cause renal tubular dysfunction, measurement of serum creatinine and urine dipstick for protein and glucose prior to drug initiation is recommended. In asymptomatic individuals, the optimal frequency for routine monitoring of creatinine and renal tubular function (urine protein and glucose) is unclear. Many Panel members monitor creatinine with other blood tests every 3 to 4 months, and 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 urine concentration of albumin, and proximal renal tubular damage increases urine concentrations of low-molecular-weight proteins like beta-2 microglobulin, the dipstick urinalysis (measuring primarily urine albumin) may be a relatively insensitive marker for TDF-associated tubular damage. Measurement of urine albumin and urine protein, and calculation of the urine albumin to urine protein ratio, can be helpful in identifying the non-albumin proteinuria that is seen in TDF-associated nephrotoxicity.[38,39] 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 April 27, 2017; last reviewed April 27, 2017)

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 (IV) 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
- [*Trizivir*] Abacavir 300 mg plus lamivudine 150 mg plus zidovudine 300 mg

## Dosing Recommendations

<table>
<tr><th colspan="2">Recommended Neonatal Dose for Treatment of HIV[a]</th></tr>
<tr><td>Weeks' Gestation at Birth</td><td>Zidovudine Oral Dosing:<br>• Twice-Daily Dosing<br>Note: For infants unable to tolerate oral agents, the IV dose should be 75% of the oral dose while maintaining the same dosing interval.</td></tr>
<tr><td>≥35 Weeks' Gestation at Birth</td><td>Birth to Age 4 Weeks:<br>• 4 mg/kg orally twice daily or alternative simplified weight band dosing<br>Simplified Weight Band Dosing for Infants Aged ≥35 Weeks:<br>Note: Provides approximately 4 mg/kg orally twice daily from birth to 4 weeks of age
<table>
<tr><th>Weight Band (kg)</th><th>Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr>
<tr><td>2 to <3 kg</td><td>1 mL</td></tr>
<tr><td>3 to <4 kg</td><td>1.5 mL</td></tr>
<tr><td>4 to <5 kg</td><td>2 mL</td></tr>
</table>
Aged >4 Weeks:<br>• 12 mg/kg orally twice daily</td></tr>
<tr><td>≥30 to <35 Weeks' Gestation at Birth</td><td>Birth to Age 2 Weeks:<br>• 2 mg/kg orally twice daily<br>Aged 2 Weeks to 6 to 8 Weeks:<br>• 3 mg/kg orally twice daily<br>Aged >6 to 8 Weeks:<br>• 12 mg/kg orally twice daily</td></tr>
</table>

## 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) 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.

## Metabolism/Elimination

- Metabolized primarily in the liver to zidovudine glucuronide, which is renally excreted.
- Zidovudine is phosphorylated intracellularly to active zidovudine-triphosphate.
- Dosing in patients with renal impairment: Dosage adjustment is required in renal

| Recommended Neonatal Dosing for Treatment of HIV[a] | |
|---|---|
| <30 Weeks' Gestation at Birth | **Birth to Age 4 Weeks:**<br>• 2 mg/kg orally twice daily<br>**Aged 4 Weeks to 8 to 10 Weeks:**<br>• 3 mg/kg orally twice daily<br>**Aged >8 to 10 Weeks:**<br>• 12 mg/kg orally twice daily |

[a] For prevention of perinatal transmission see Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.

**Infant/Child Dose (Age ≥35 Weeks Post-Conception and ≥4 Weeks Post-Delivery with Body Weight ≥4 kg):**

**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/$m^2$ body surface area every 12 hours

**Adolescent (Aged ≥18 Years) and Adult Dose:**

- 300 mg twice daily

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

*Adolescent (Weight ≥30 kg) and Adult Dose:*

- 1 tablet twice daily

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

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

- 1 tablet twice daily

insufficiency.

- Dosing in patients with hepatic impairment: Decreased dosing may be required in patients with hepatic impairment.
- Do not use fixed-dose combination products (e.g., Combivir, Trizivir) in patients with creatinine clearance <50 mL/min, on dialysis, or who have impaired hepatic function.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents)

- *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 affecting 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. Incidence of neutropenia may be increased in infants receiving lamivudine.[1]
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. 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.[2] Possible increased risk of cardiomyopathy.[3] Possible association between first-trimester exposure to zidovudine and congenital heart defects (see Teratogenicity in the Perinatal Guidelines).[4-6]

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ zidovudine.html).

***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 abacavir, didanosine, or lamivudine.[7-23] Pediatric experience with zidovudine both for treatment of HIV and for prevention of perinatal transmission is extensive.

*Efficacy in Clinical Trials*

**Zidovudine in Combination with Lamivudine**

- Zidovudine with lamivudine has been extensively studied in children and has been a part of ART regimens in many trials.
- Zidovudine combined with lamivudine was compared to abacavir plus lamivudine and stavudine plus 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.[24]

**Zidovudine in Combination with Abacavir or Didanosine**

- In a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities.[25]
- 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.[26,27]

*Special Issues in Neonates*

Perinatal trial PACTG 076 established that zidovudine prophylaxis given during pregnancy, labor, and delivery, and to the newborn reduced risk of perinatal transmission of HIV by nearly 70%[28] (see the Perinatal Guidelines 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 (prophylactic dose) is recommended for neonates/infants ≥35 weeks' gestation for prevention of transmission (see the Perinatal Guidelines). Infants who are HIV-exposed but uninfected should be continued on the prophylactic dose for 4 to 6 weeks depending on assessment of risk for perinatal transmission and gestational age at time of delivery (see Perinatal Guidelines).

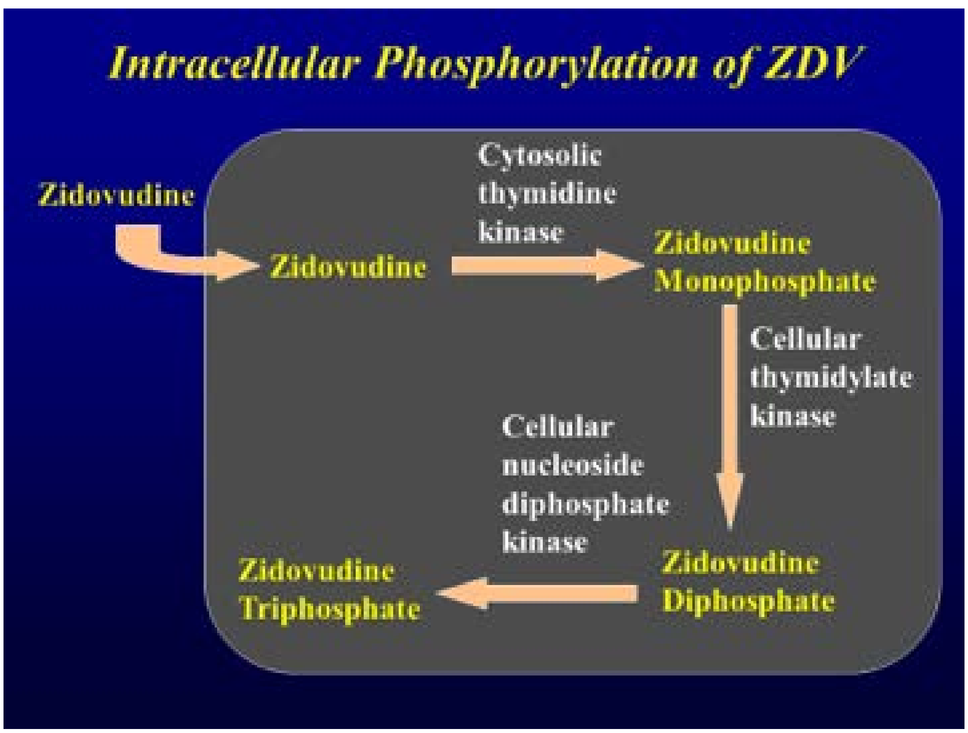
For full-term neonates who are diagnosed with HIV, the zidovudine dose should be increased at age 4 weeks to the continuation dose (see dosing table). The activity of the enzymes responsible for glucuronidation is low at birth and increases dramatically over the first 4 to 6 weeks of life in full-term neonates.

For premature infants who are diagnosed with HIV infection, the time to change the dose to continuation dose varies with post-gestational age and clinical status of the neonate. Based on modeling and pharmacokinetics (PK) of zidovudine in premature infants, for infants born at ≥30 to <35 weeks change to 12 mg/kg/dose at post-gestational age 6 to 8 weeks and for infants <30 weeks, change to 12 mg/kg at post-gestational age 8 to 10 weeks.[29] Careful clinical assessment of the infant, evaluation of hepatic and renal function, and review of concomitant medications should be performed prior to increasing zidovudine dose to that recommended for full-term infants.

***Pharmacokinetics***

Overall, zidovudine PK in pediatric patients aged >3 months are similar to those 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 low intracellular zidovudine triphosphate concentrations seen with 600-mg, once-daily dosing in adolescents.[30] PK studies such as PACTG 331 demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with term newborns of similar postnatal age.[8] 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.[19]

**Figure A: Intracellular Phosphorylation of ZDV**




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 is the 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% when compared on post-delivery day 1 to day 28, whereas the zidovudine diphosphate and zidovudine triphosphate remained low throughout the sampling period.[31] Based on the poor correlation between zidovudine dose and intracellular zidovudine triphosphate concentrations, a simplified dosing approach for infants ≥35 weeks gestation receiving approximately 4 mg/kg twice daily oral dosing for the first 4 weeks of life is proposed (see dosing table). These volumes provide approximately 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 ZDV 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.[7,8,32]

Incidence of hematological toxicity was compared in the ARROW study of Ugandan/Zimbabwean treatment-naive children randomized to zidovudine- versus abacavir-containing regimens. The incidence of severe anemia was similar regardless of zidovudine use and suggests that advanced HIV disease contributed to low hemoglobin values. Zidovudine use was associated with severe neutropenia in a small number of children.[33]

Zidovudine is associated with greater mitochondrial toxicity when compared to abacavir and tenofovir disoproxil fumarate but less than stavudine.[34,35]

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.[3] Recent analysis of data from a US-based, multicenter prospective cohort study (PACTG 219/219C) found that ongoing zidovudine exposure was independently associated with a higher rate of cardiomyopathy.[3]

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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 April 27, 2017; last reviewed April 27, 2017)

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

## Dosing Recommendations

### Neonatal Dose:

- Efavirenz is not approved for use in neonates.

### Pediatric Dose:

*Infants and Children Aged 3 Months to <3 Years and Weighing ≥3 kg:*

- The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that efavirenz generally not be used in children aged 3 months to <3 years. If use of efavirenz is unavoidable due to the clinical situation, the Panel suggests the use of investigational doses of efavirenz in this age group. See text for investigational dosing tables; evaluation of CYP 2B6 genotype is required prior to use. Therapeutic drug monitoring should be considered with an efavirenz plasma concentration measured 2 weeks after initiation; some experts would also measure at age 3 years after making the transition to the new dose (see text under therapeutic drug monitoring at the bottom of this section). For dose adjustment based on efavirenz concentrations, consultation with an expert is recommended.

*Children Aged ≥3 Years and Weighing ≥10 kg:*

**Note:** See Tables 1a and 1b in text for recommended dosing if EFV must be used in children aged <3 years

## 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, 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. Consider alternatives to efavirenz when co-administered with a drug with known risk of *Torsades de Pointes* or when administered to patients at higher risk of *Torsades de Pointes*

## Special Instructions

- Efavirenz can be swallowed as a whole capsule or tablet or administered by sprinkling the contents of an opened capsule on food as described below.
- Administer whole capsule or tablet of Atripla on an empty stomach. Avoid administration with a high-fat meal because of potential for increased absorption.
- Bedtime dosing is recommended, particularly during the first 2 to 4 weeks of therapy, to improve tolerability of central nervous system side effects.
- Efavirenz should be used with caution in female adolescents and adults with reproductive potential because of the potential risk of teratogenicity.

**Administer Efavirenz Once Daily**

| Weight (kg) | Efavirenz Dose (mg)[a,b] |
|---|---|
| 10 kg to <15 kg | 200 mg |
| 15 kg to <20 kg | 250 mg |
| 20 kg to <25 kg | 300 mg |
| 25 kg to <32.5 kg | 350 mg |
| 32.5 kg to <40 kg | 400 mg |
| ≥40 kg | 600 mg |

[a] The dose in mg can be dispensed in any combination of capsule strengths.

[b] Some experts recommend a dose of 367 mg/$m^2$ body surface area (maximum dose 600 mg) because of concern for under-dosing, especially at the upper end of each weight band (see Pediatric Use for details).

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

- 600 mg once daily

**[*Atripla*] Efavirenz plus Emtricitabine plus TDF**

- Atripla should not be used in pediatric patients <40 kg as the efavirenz dose of 600 mg would be excessive.

*Adult Dose:*

- One tablet once daily

**Instructions for Use of 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*.
- Dosing of efavirenz in patients with hepatic impairment: No recommendation is currently available; use with caution in patients with hepatic impairment.
- Adult dose of Atripla in patients with renal impairment: Because Atripla is a fixed-dose combination product and TDF and emtricitabine require dose adjustment based on renal function, Atripla should not be used in patients with creatinine clearance <50 mL/minute or in patients on dialysis.
- Interpatient variability in efavirenz exposure can be explained in part by polymorphisms in CYP450 with slower metabolizers at higher risk of toxicity (see text for information about therapeutic drug monitoring for management of mild or moderate toxicity).

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Co-administration of efavirenz with drugs primarily metabolized by CYP2C9, 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 are multiple drug interactions. Importantly, dosage adjustment or the addition of ritonavir may be necessary when efavirenz is used in combination with atazanavir, fosamprenavir, ritonavir-boosted lopinavir (LPV/r), or maraviroc.
- Before efavirenz is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with efavirenz.

- QTc prolongation has been observed with the use of efavirenz.[1,2] Consider alternatives to efavirenz when coadministered with a drug with known risk of *Torsades de Pointes* or when administered to patients 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, seizures, primarily reported in adults.
- *Rare:* QTc prolongation has been observed with the use of efavirenz.[1,2] A case report associated efavirenz use with marked QT prolongation and *Torsades de Pointes*.[3] An association between efavirenz and suicidal ideation, suicide, and attempted suicide (especially among those with a history of mental illness or substance abuse) was found in one retrospective analysis of four comparative trials in adults. This association, however, was not found in analyses of two large observational cohorts.
- *Potential risk of teratogenicity:* For discussion, see Pediatric Use section below; see also Efavirenz in the Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in The United States (Perinatal Guidelines).

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

Efavirenz is Food and Drug Administration (FDA)-approved for use as part of antiretroviral therapy in children aged ≥3 months who weigh at least 3.5 kg.

*Efficacy in Clinical Trials*

In clinical trials in adults and children with HIV, efavirenz in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) has been associated with excellent virologic response.

- Efavirenz-based regimens have proven virologically superior or non-inferior to a variety of regimens in adults including those containing LPV/r, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.[4-10]
- Efavirenz proved inferior to dolutegravir in the SINGLE trial in adults, which compared virologic response of dolutegravir in combination with abacavir and lamivudine to efavirenz combined with tenofovir disoproxil fumarate and emtricitabine at weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.[11]
- Efavirenz in combination with two NRTIs or with a NRTI and a protease inhibitor has been studied in children with virologic potency and safety comparable to what is seen in adults.[12-18]

*Pharmacokinetics: Pharmacogenomics*

Efavirenz metabolism is controlled by enzymes that are polymorphically expressed and result in large interpatient variability in drug exposure. CYP2B6 is the primary enzyme for efavirenz metabolism, and pediatric patients with the CYP 2B6 516 T/T genotype (which has an allele frequency of 20% in African Americans) have reduced metabolism resulting in higher efavirenz levels compared with those with the G/G or G/T genotype.[19-22] IMPAACT P1070 has shown that aggressive dosing with approximately 40 mg/

kg using opened capsules resulted in therapeutic efavirenz concentrations in 68% of children aged <3 years with G/G or G/T genotype but excessive exposure in those with T/T genotype.[21] Optimal dosing may require pretreatment CYP2B6 genotyping in children aged <3 years (see discussion below).[21,23] Additional variant CYP2B6 alleles and variant CYP2A6 alleles have been found to influence efavirenz concentrations in adults and children.[24-28]

*Pharmacokinetics and Dosing: Infants and Children Aged <3 Years*

The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends that efavirenz generally not be used 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.[21,29] 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.[22] This maturation of oral clearance is postulated to result from an increase in the expression of CYP 2B6 with age.[22] CYP 2B6-516-G/G genotype is associated with the greatest expression of hepatic CYP 2B6 when compared with the CYP 2B6-516-G/T or -T/T genotype.[19] In children with CYP 2B6-516-G/G genotype, the oral clearance rate has been shown to be higher in children aged <5 years than in older children.[19] Efficacy data for opened capsules with contents used as sprinkles suggest acceptable palatability and bioavailability for infants and children aged <3 years. IMPAACT study P1070, an ongoing study of children with HIV and HIV/tuberculosis coinfection aged <3 years, using efavirenz dosed by weight band based on CYP2B6 GG/GT versus T/T genotype (see Tables 1a and 1b below), resulted in HIV RNA <400 copies/mL in 61% by intent to treat analysis at 24 weeks.[21] 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.[21] Therefore, dosing tables have been modified so that infants and young children with T/T genotype will receive a reduced dose. Additional subjects will be studied to confirm that this dose is appropriate for this subset of patients. The modified doses listed in Tables 1a and 1b are under investigation.

*Investigational Dosing for Children Aged 3 Months to <3 Years Based on CYP 2B6 Genotype*

**Table 1a. Protocol P1070 Dosing for Patients with CYP 2B6 516 GG and GT Genotypes (Extensive Metabolizers [EM])[a]**

| Weight (kg) | Efavirenz Dose (mg) |
|---|---|
| 3 kg to <5 kg | 200 mg |
| 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 1b. Protocol P1070 Dosing for Patients with CYP 2B6 516 TT Genotype (Slow Metabolizers [SM])[a]**

| Weight (kg) | Efavirenz Dose (mg) |
|---|---|
| 3 kg to <7 kg | 50 mg |
| 7 kg to <14 kg | 100 mg |
| 14 kg to <17 kg | 150 mg |
| ≥17 kg | 150 mg |

[a] Investigational doses are based on IMPAACT study P1070.[21] Evaluation of CYP 2B6 genotype is required. Therapeutic drug level monitoring is recommended with a trough measured 2 weeks after initiation 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 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 2).

**Table 2: FDA-Approved Dosing for Children Aged 3 Months to <3 Years (Without Regard to CYP 2B6 Genotype)**

| Weight (kg) | Efavirenz Dose (mg) |
|---|---|
| 3.5 kg to <5 kg | 100 mg |
| 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 CYP 2B6 extensive metabolizer doses and higher than the CYP 2B6 slow metabolizer 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 under-dosing in CYP 2B6 extensive metabolizers. Estimates of efavirenz area under the curve (AUC) for FDA dosing using P1070 data are given in Table 3.[23] Estimates were calculated as follows: P1070 observed AUC X (FDA dose/P1070 CYP 2B6 genotype-directed study dose). 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.[23] Estimates indicate that FDA-recommended doses of efavirenz will produce excessive efavirenz AUCs in 67% of slow metabolizer (SM) and sub-therapeutic AUCs in 33% of extensive metabolizer (EM) children aged <3 years, whereas CYP 2B6 genotype-directed dosing resulted in achievement of target AUCs in 83% of EM children and 89% of SM children.

**Table 3: Estimated Efavirenz AUC for FDA Dosing Compared with AUC for P1070 Dosing[a]**

| Metabolizer Phenotype | Median AUC (mcg*h/mL) [95% CI] | Number with Estimated Plasma AUC <35 mcg*h/mL | Number with Estimated Plasma AUC 35–180 mcg*h/mL | Number with Estimated Plasma AUC >180 mcg*h/mL |
|---|---|---|---|---|
| **EM (CYP2B6 516 GG/GT) n = 30** | | | | |
| P1070 Dosing[b] | 105.6 [58.5, 129.6] | 4 (13%) | 25 (83%) | 1 (3%) |
| FDA Dosing[c] | 52.8 [29.4, 64.8] | 10 (33%) | 19 (63%) | 1 (3%) |
| **SM (CYP2B6 516 TT) n = 9** | | | | |
| P1070 Dosing[b] | 122.6 [93.2, 162.6] | 0 (0%) | 8 (89%) | 1 (11%) |
| FDA Dosing[c] | 245.1 [162.2, 325.1] | 0 (0%) | 3 (33%) | 6 (67%) |

[a] Moore CB, et al. Abstract 903. Presented at: 20th Conference on Retroviruses and Opportunistic Infections (CROI). 2014. Boston, MA
[b] Observed values
[c] Predicted values

**Key to Acronyms:** AUC = area under the curve; CYP = cytochrome P450; EM = extensive metabolizer; FDA = Food and Drug Administration; SM = slow metabolizer

The Panel recommends that efavirenz generally not be used in children aged 3 months to <3 years. If the clinical situation demands use of efavirenz, Panel members recommend determining CYP2B6 genotype (a list of laboratories performing this testing is available at http://www.ncbi.nlm.nih.gov/gtr/labs). Patients should be classified as extensive CYP 2B6 516 G/G and G/T genotypes versus slow CYP 2B6 516 T/T genotype metabolizers to guide dosing as indicated by the investigational doses from IMPAACT study P1070 (see Tables 1a and 1b). Whether the doses used are investigational or FDA-approved, measuring efavirenz plasma concentrations should be considered 2 weeks post-initiation (see Role of Therapeutic Drug Monitoring). For dose adjustment, consultation with an expert is recommended. In addition, when dosing 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 ≥3 Years and Adolescents*

Long-term HIV RNA suppression has been associated with a mid-dosing interval concentration ($C_{12}$) of efavirenz of >1 mg/L in adults[30] although some question whether use of a single target value is valid, especially in adherent patients.[31] Early HIV RNA suppression in children has also been seen with higher drug concentrations. Higher efavirenz troughs of 1.9 mg/L were seen in children with HIV RNA levels ≤400 copies/mL versus efavirenz troughs of 1.3 mg/L in children with detectible virus (>400 copies/mL).[32] In a West African pediatric study, ANRS 12103, early reduction in viral load (by 12 weeks) was greater in children with efavirenz minimum plasma concentration ($C_{min}$) levels >1.1 mg/L or AUC >51 mcg*h/mL.[33]

Even with the use of FDA-approved pediatric dosing in children aged ≥3 years, efavirenz concentrations can be suboptimal.[19,33-37] 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 efavirenz dose was 13 mg/kg (367 mg/m$^2$) and the range was from 3 to 23 mg/kg (69–559 mg/m$^2$).[32] A PK study in 20 children aged 10 to 16 years treated with LPV/r 300 mg/m$^2$ twice daily plus efavirenz 350 mg/m$^2$ 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.[38]

*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 compared with 27% of adults. 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 1 meta-analysis of randomized trials.[39] 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 400 mg of efavirenz is associated with fewer AEs but non-inferior virologic response when compared with the recommended 600-mg dose of efavirenz in adults. Despite these findings, a reduction in efavirenz dose in adults is not recommended as part of initial treatment.[40,41] 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.[42,43] This association, however, was not found in analyses of 2 large observational cohorts[44,45] and no cases of suicide were reported in a systematic review of randomized trials.[39] 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.[30,46-49] In patients with pre-existing psychiatric conditions, efavirenz should be used cautiously. Adverse CNS AEs occurred in 14% of children receiving efavirenz in clinical studies[50] and in 30% of children with efavirenz concentrations greater than 4 mcg/mL.[20] CNS AEs may be harder to detect in children because of the difficulty in assessing 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.[30,46] Homozygous carriers of the CYP2B6*6 allele (CYP2B6*6/*6) may be at increased risk for efavirenz-induced rate corrected QT (QTc) prolongation. The CYP2B6*6 allele codes for the CYP2B6 516 G>T complementary DNA nucleotide change.[51] The effect of efavirenz on the QTc interval was evaluated in a study in 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 a 600-mg daily dose for 14 days.[1] Drugs that prolong the mean QTc interval by more than 20 ms have a substantially increased likelihood of being pro-arrhythmic. While the data on drugs that prolong the mean QTc interval by more than 5 ms but less than 20 ms are inconclusive, some of these drugs have been associated with pro-arrhythmic risk.[52] Alternatives to efavirenz should be considered when coadministered with a drug with known risk of *Torsades de Pointes*, for example quinidine or clarithromycin, or when administered to patients at higher risk of *Torsades de Pointes*.[2]

*Toxicity: Potential Risk of Teratogenicity*

In prior Perinatal Guidelines, efavirenz use was not recommended before 8 weeks' gestational age, because of concerns regarding potential teratogenicity. Although this caution remains in the package insert, a large meta-analysis has been reassuring that risks of neural tube defects after first-trimester efavirenz exposure are not greater than those in the general population.[2,53] 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 ARV drugs in pregnancy (which note that efavirenz can be used throughout pregnancy).[54,55] 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.[56]

*Therapeutic Drug Monitoring*

**Note:** See Role of Therapeutic Drug Monitoring section.

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.[57,58] 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 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 for 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 ($C_{12}$) greater than 1 mg/L in adults and concentrations >4.0 mg/L are associated with CNS side effects.[30] A recent study in children showed that a higher proportion of children with a $C_{12}$ <1 mg/L had evidence of viral replication compared to those with a $C_{12}$ >1 mg/L.[59] However, the validity of use of a single target has been called into question.[31] In addition, a lower limit $C_{12}$ >0.7mg/L was most predictive of virologic outcome in a study of 180 adults.[60]

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# Etravirine (ETR, Intelence, TMC 125) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 ≥16 kg)**

| Body Weight Kilogram (kg) | 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 |
| ≥30 kg | 200 mg twice |

### 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.
- Patients unable to swallow etravirine tablets may disperse the tablets in liquid, as follows: 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°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.
- Dosing of etravirine in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.

- Dosing of etravirine in patients with renal impairment: Dose adjustment is not required in patients with renal impairment.

## 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.
- Multiple interactions with antiretroviral agents and other drugs (see text below)

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- 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, or rilpivirine). Limited data in adults suggest that etravirine may reduce the trough concentration of raltegravir,[1] but no dose adjustment is currently recommended when etravirine and raltegravir are used together. Etravirine significantly reduces plasma concentrations of dolutegravir; dolutegravir should only be used with etravirine when co-administered with atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir.

***Major Toxicities***

- *More common:* Nausea, diarrhea, and mild rash. Rash occurs most commonly in 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 including Stevens Johnson syndrome, hypersensitivity reactions (HSRs) (including constitutional findings and sometimes organ dysfunction including hepatic failure), and erythema multiforme have been reported. 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

Etravirine is Food and Drug Administration-approved for use in ARV-experienced children and adolescents aged 6 to 18 years.

*Efficacy in Clinical Trials*

- In the PIANO study[4], ARV-experienced children aged 6 to <18 years received etravirine with a ritonavir-boosted HIV-1 PI as part of an optimized background regimen. At Week 24, 67% of these pediatric participants had plasma HIV-1 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 CD4 cell count from baseline of 156 cells/mm$^3$. A greater fraction of children aged 6 to <12 years had plasma HIV-1 RNA <50 copies/mL than adolescents aged 12 to <18 years (68% versus 48%).
- In a retrospective study of 23 adolescents and young adults conducted by Briz et al., 78% achieved an HIV-1 RNA <50 copies/mL at a median of 48.4 weeks of follow-up.[2]

***Pharmacokinetics***

In a Phase I dose-finding study involving children aged 6 to 17 years, 17 children were given 4 mg/kg etravirine twice daily. The PK parameters $AUC_{12h}$ and minimum plasma concentration ($C_{min}$) were below preset statistical targets based on prior studies involving adults.[3] Based on acceptable PK parameters, the higher dose (5.2 mg/kg twice daily; maximum 200 mg per dose) was chosen for evaluation in the Phase II PIANO study. Exposures remained lower in older adolescents than in adults and younger children, and Asians compared to either white or black participants.[4]

**Pharmacokinetics of Etravirine**

| | Mean $AUC_{0\text{-}12h}$ (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:** $AUC_{0\text{-}12h}$ = Area under the curve for 12 hours post-dose; $C_{0h}$ = pre-dose concentration during chronic administration

Etravirine is often combined with darunavir/ritonavir for treatment of adults with HIV infection with prior virologic failure. Cressey et al. examined PK data from 36 adolescents and young adults receiving etravirine 200 mg bid in combination with darunavir/ritonavir 600 mg/100 mg twice daily. The pharmacokinetic exposures of both agents were similar to those seen in adults, although with high inter-individual variability.[5] The pharmacokinetics of both drugs were also studied in adolescents and young adults receiving darunavir/ritonavir 800 mg/100 mg once daily with either etravirine 200 mg twice daily or etravirine 400 mg once daily.[6] Darunavir concentrations were higher when coadministered with etravirine, particularly when the latter was given 200 mg twice daily. Etravirine exposures were lower, particularly when given twice daily, although the authors commented on the limited sample size involved in these studies. While the combination of etravirine and darunavir/ritonavir has been effective in a small cohort of adolescents with HIV infection,[7] and in 51% of participants in the PIANO study,[4] 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, panel members recommend 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 4 (4%) individuals, all of whom were female. Diarrhea occurred in 3 (3%) and was only reported in adolescents.

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# Nevirapine (NVP, Viramune) (Last updated April 27, 2017; last reviewed April 27, 2017)

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:** No longer available in the United States

## Dosing Recommendations

**Neonate/Infant Dose (≤14 Days) for Prevention:**

- See Infant Antiretroviral Prophylaxis and Neonatal Antiretroviral Drug Dosing of the Perinatal Guidelines for dosing.

**Treatment of HIV Infection:**
*Pediatric Dose: Immediate Release and Suspension Formulations*

- In most situations, nevirapine is given once daily for 2 weeks to allow for autoinduction of enzymes involved in its metabolism. This may not be necessary in children aged <2 years. See text and footnote.[a]

*Aged <1 Month (**Investigational dose** not Food and Drug Administration approved):*

- 34–37 weeks gestational age (no lead in; please see text and footnote[a]): 4 mg/kg/dose twice daily for the first week increasing to 6 mg/kg/dose twice daily thereafter
- ≥37 weeks gestational age to <1 month: 6 mg/kg/dose twice daily (no lead in; please see text and footnote[a])
- See Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants

*Aged ≥1 Month to <8 Years:*

- 200 mg/m² of body surface area (BSA)/dose twice daily after lead-in dosing.[a] In children aged ≤2 years, some experts initiate nevirapine without a lead-in (maximum dose of immediate-release tablets is 200 mg twice daily).

*Aged ≥8 Years:*

- 120–150 mg/m² BSA/dose twice daily after lead-in dosing[a] (maximum dose of immediate-release tablets is 200 mg twice daily.)
- When adjusting the dose for a growing child,

## Selected Adverse Events

- Rash, including Stevens-Johnson syndrome
- Symptomatic hepatitis, including fatal hepatic necrosis
- 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 Major Toxicities section).
- 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 dosing should be restarted with once-daily dosing for 14 days, followed by escalation to the full, twice-daily regimen (see Dosing Considerations: Lead-In Requirement).
- Most cases of nevirapine-associated hepatic toxicity occur during the first 12 weeks of therapy; frequent clinical and laboratory monitoring, including liver function tests, is important during this period (see Major Toxicities).

## Metabolism/Elimination

- Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine 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$^2$ dosage as the child grows, as long as there are no untoward effects.

| BSA Range (m$^2$) | NVP XR (mg) |
|---|---|
| 0.58–0.83 | 200 mg once daily (2 x 100 mg) |
| 0.84–1.16 | 300 mg once daily (3 x 100 mg) |
| ≥1.17 | 400 mg once daily (1 x 400 mg) |

**Key to Abbreviations:** BSA = body surface area; NVPXR = nevirapine extended release

### Pediatric Dose Extended-Release Formulation (≥6 Years):

- Patients ≥6 years who are already taking immediate-release nevirapine twice daily can be switched to nevirapine extended release without lead-in dosing. Please see footnote.[a]

### Adolescent and Adult Dose:

- 200 mg twice daily or 400 mg extended release once daily.

### Nevirapine in Combination with Lopinavir/ Ritonavir:

A higher dose of ritonavir-boosted lopinavir may be needed (see Ritonavir-Boosted Lopinavir section).

(glucuronidated metabolites).

- Dosing of nevirapine in patients with renal failure receiving hemodialysis: An additional dose of nevirapine should be given following dialysis.
- Dosing of nevirapine in patients with hepatic impairment: Nevirapine should not be administered to patients with moderate or severe hepatic impairment.

[a] Nevirapine is usually initiated at a lower dose and increased in a stepwise fashion to allow induction of cytochrome P450 metabolizing enzymes, which results in increased drug clearance. The occurrence of rash is diminished by this stepwise increase in dose. 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 Dosing: Special Considerations: Neonates ≤14 Days and Premature Infants). In patients 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.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Induces hepatic cytochrome P450 including 3A (CYP3A) and 2B6; auto-induction of metabolism occurs in 2 to 4 weeks, with a 1.5- to 2-fold increase in clearance. There is potential for multiple drug interactions. Mutant alleles of CYP2B6 cause increases in nevirapine serum concentration in a similar manner—but to a lesser extent—than efavirenz. Altered adverse effect profiles related to elevated nevirapine levels have not been documented probably because there are alternative CYP metabolic pathways for nevirapine[1]; however, CYP2B6 polymorphisms can vary greatly among populations, which may account for differences in drug exposure. Please see Efavirenz section for further details.

- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions. **Nevirapine should not be co-administered to patients receiving atazanavir (with or without ritonavir). Nevirapine increases the metabolism of lopinavir and dosage adjustment is**

**recommended** (see Lopinavir/Ritonavir section).

### *Major Toxicities*

**Note:** These are seen with continuous dosing regimens, not single-dose nevirapine prophylaxis.

- *More common:* Skin rash (some severe and requiring hospitalization; some life-threatening, including Stevens-Johnson syndrome and toxic epidermal necrolysis), fever, nausea, headache, and abnormal hepatic transaminases. Nevirapine should be permanently 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 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 a patient's overall ability to tolerate the regimen and the current antiviral response.
- *Less common (more severe):* Severe, life-threatening, and in rare cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure (these 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$^3$ in adult females and >400 cells/mm$^3$ in adult males). In children, there is a 3-fold increased risk of rash and hepatotoxicity when children initiate nevirapine with a CD4 percentage >15%.[2] 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 permanently 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR).

### *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.[3-11] 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 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 an NNRTI-based and PI-based regimen.[12-18]

In infants and children previously exposed to single-dose nevirapine for prevention of perinatal transmission; nevirapine-based antiretroviral therapy (ART) is less likely than LPV/r-based ART to control virus load. In a large randomized clinical trial, P1060, 153 children (mean age 0.7 years) previously exposed to nevirapine for perinatal prophylaxis were treated with zidovudine plus lamivudine plus the randomized addition of nevirapine versus 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 12–24 or HIV RNA >400 copies/mL at Week 24) compared with 7% in the zidovudine/lamivudine/LPV/r arm, $P = 0.0009$. When all primary endpoints were considered, including viral failure, death, and treatment discontinuation, the protease inhibitor (PI) arm remained superior because 40% of children in the nevirapine arm met a primary endpoint versus 22% for the LPV/r arm, $P = 0.027$.[15] Similar results were reported in a comparison study of nevirapine versus LPV/r in children aged 6 to 36 months **not** previously exposed to nevirapine, suggesting that lopinavir/ritonavir-based therapy is superior to nevirapine-based therapy for infants, regardless of past nevirapine exposure.[12]

Extended-release nevirapine (400-mg tablets) was approved by the FDA for use in children aged ≥6 years in November 2012. Trial 1100.1518 was an open-label, multiple-dose, non-randomized, crossover trial performed in 85 pediatric participants with HIV aged 3 years to <18 years who had received at least 18 weeks of immediate-release nevirapine and had plasma HIV-1 RNA <50 copies per mL prior to trial enrollment. Participants were stratified according to age (3 to <6 years, 6 to <12 years, and 12 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.[19] 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-1 RNA <50 copies per mL.[20]

***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 non-nucleoside reverse transcriptase inhibitor resistance to both nevirapine and efavirenz. Younger children (≤8 years of age) have higher apparent oral clearance than older children and require a higher dosage to achieve equivalent drug exposure compared with children aged >8 years.[8,9] Because of this, it is recommended that dosing for children aged <8 years be 200 mg/m$^2$ of BSA per dose when given twice daily (immediate-release tablet maximum dose 200 mg twice daily) or 400 mg/m$^2$ of BSA per dose when administered once daily as the extended-release preparation (maximum dose of the extended-release preparation 400 mg/dose once daily). For children aged ≥8 years, the recommended dose is 120 mg/m$^2$ of BSA per dose (maximum dose 200 mg) administered twice daily to a maximum of 400 mg once daily when the extended-release preparation is used in children aged ≥6 years. When adjusting the dose in a growing child, the milligram dose need not be decreased (from 200 mg/m$^2$ to 120 mg/m$^2$) 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$^2$ dosage as the child grows. Some practitioners dose nevirapine at 150 mg/m$^2$ of BSA every 12 hours or 300 mg/m$^2$ per dose once daily if using the extended-release preparation (maximum of 200 mg per dose twice daily of the immediate-release tablets or 400 mg per dose once daily of 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 (200 mg/m$^2$ in infants ≥15 days and children <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, largely in adult cohorts, previously indicated the potential for greater drug toxicity without this lead-in.[21] The CHAPAS-1 Trial[22] randomized 211 children to initiate ART with nevirapine without a lead-in (age-appropriate dose, twice daily, of the immediate-release preparation) or with a lead-in (age-appropriate dose, once daily, of the immediate-release preparation) for 2 weeks followed by standard twice-daily dosing of the immediate-release preparation. Children were followed for a median of 92 weeks (68–116), and there was no difference in grade 3 or 4 adverse events between the 2 groups. The group initiating 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. In a substudy of this trial, the investigators evaluated nevirapine plasma concentrations 3 to 4 hours after a morning dose of nevirapine after 2 weeks of therapy. For children aged <2 years, 13% (3/23) initiating at full dose versus 32% (7/22) initiating at half dose had sub-therapeutic nevirapine levels (<3 mg/L) at 2 weeks ($P$ = 0.16). There were no rash events in the substudy group aged <2 years and in the parent CHAPAS study there was a strong age effect on rash occurrence (increased risk with increasing age), suggesting that a lead-in dose may not be necessary in young patients.[23] Reinitiating half-dose nevirapine for another 2 weeks in children who have interrupted therapy for 7 days or longer has been standard practice; however, given the current understanding of nevirapine resistance, the half-life of the CYP enzymes,[24] and the results of CHAPAS-1, the Panel recommends restarting full-dose nevirapine in children who interrupt therapy for 14 days or less.

***Dosing: Special Considerations: Neonates and Premature Infants***

For neonates and for premature infants (until 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. Based on PK modeling, an investigational nevirapine dose of 6 mg/kg administered twice daily has been proposed for full-term infants diagnosed as infected in the first few days of life.[25-28] However, a dose of 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 6 mg/kg/dose 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 the majority of infants with trough concentrations of nevirapine greater than 3 mcg/ mL.[29] Providers considering treatment of infants <2 weeks or premature infants should contact a pediatric HIV expert for guidance because the decision about whether to treat and what 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 April 27, 2017; last reviewed April 27, 2017)

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

## 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 ≥35 kg, see the Pharmocokinetics section below.

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

*Antiretroviral-Naive Patients with HIV RNA ≤100,000 copies/mL or Virologically-Suppressed (HIV RNA <50 copies/mL) Patients with No History of Virologic Failure or Resistance to Rilpivirine and Other Antiretroviral (ARV) Drugs and Currently on Their First or Second Regimen:*

- 25 mg once daily

### Combination Tablet

*[Complera] Emtricitabine plus Rilpivirine plus TDF*

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

- 1 tablet once daily in treatment-naive patients with baseline viral load <100,000 copies/mL or to replace a stable ARV regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Complera, and currently on their first or second regimen.

*[Odefsey] Emtricitabine plus Rilpivirine plus TAF*

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

- 1 tablet once daily with a meal as initial therapy in those with no antiretroviral treatment history with HIV-1 RNA less than

## Selected Adverse Events

- Depression
- Insomnia
- Headache
- Rash (can be severe and include Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS])
- Hepatotoxicity
- Altered ACTH stimulation test of uncertain clinical significance

## Special Instructions

- 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 either at least 2 hours before or at least 4 hours after rilpivirine.
- Use rilpivirine with caution when co-administered with a drug with a known risk of *Torsades de Pointes* (see https://www.crediblemeds.org/).
- Do not start rilpivirine in patients with HIV RNA >100,000 copies/mL because of increased risk of virologic failure.

## Metabolism/Elimination

- Cytochrome P450 (CYP) 3A substrate
- Dosing in patients with hepatic impairment: No dose adjustment is necessary in patients

or equal to 100,000 copies per mL; or to replace a stable ART regimen in those who are virologically-suppressed (HIV-1 RNA <50 copies per mL) for at least 6 months with no history of treatment failure and have no known current or past substitutions associated with resistance to the individual components of Odefsey.

with mild or moderate hepatic impairment.

- Rilpivirine decreases tubular secretion of creatinine and slightly increases measured serum creatinine, but does not affect glomerular filtration.
- Dosing in patients with renal impairment: No dose adjustment is required in patients with mild or moderate renal impairment.
- Complera (fixed-dose combinations) should not be used in patients with CrCl <50 mL/min or in patients requiring dialysis.
- Use rilpivirine with caution in patients with severe renal impairment or end-stage renal disease. Increase monitoring for adverse effects because rilpivirine concentrations may be increased in patients with severe renal impairment or end-stage renal disease.
- When using Complera see the tenofovir disoproxil fumarate section; when using Odefsey see the tenofovir alafenamide section.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Rilpivirine is a CYP 3A substrate and requires dosage adjustments when administered with CYP 3A-modulating medications.
- Before rilpivirine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions.
- Co-administration of rilpivirine with drugs that increase gastric pH may decrease plasma concentrations of rilpivirine.
- Antacids should only be taken either 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.

***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 adolescent studies, 6/30 (20%) developed this abnormality.[1] The clinical significance of these results is unknown.

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug

Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

With the viral load and antiretroviral (ARV) resistance restrictions noted above, rilpivirine in combination with other antiretroviral agents,[1] the combination tablet rilpivirine/emtricitabine/tenofovir disoproxil fumarate (Complera)[2] and the combination tablet rilpivirine/emtricitabine/tenofovir alafenamide (TAF) (Odefsey) are Food and Drug Administration-approved in persons aged ≥12 years and weighing >35 kg.[3]

*Efficacy in Clinical Trials*

A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in 2 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 ≥100,000 copies/mL receiving rilpivirine had higher rates of virologic failure compared to those receiving efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral load ≤100,000 copies/mL.[4-7]

A study of rilpivirine, 25 mg daily in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-naive adolescents aged 12 to 18 years, demonstrated that the regimen was well tolerated over 48 weeks. Among adolescents with baseline viral loads ≤100,000 copies/mL, 86% had a virologic response at 24 weeks and 79% at 48 weeks. Among adolescents with baseline viral loads >100,000 copies/mL, 38% had a virologic response at 24 weeks and 50% at 48 weeks.[8]

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 usefullness for some adolescents with an irregular schedule. Odefsey is a small pill, and can be useful for select patients who do not have any drug resistance mutations who might want to switch from a multi-pill regimen.

*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 ≥17 kg (ClinicalTrials.gov identifier NCT00799864). The Panel considers that rilpivirine may be appropriate in select children aged <12 years as long as they weigh ≥35 kg; an expert in pediatric HIV infection should be consulted.

An international (India, Thailand, Uganda, and South Africa) Phase II trial, PAINT TMC278, investigated a 25-mg dose of rilpivirine in combination with 2 NRTIs in ARV-naive adolescents aged 12 to <18 years who weigh ≥32 kg and have a viral load ≤100,000 copies/mL.[8] In the dose-finding phase of the study, 11 youth aged >12 to ≤15 years and 12 youth aged >15 to ≤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.[9]

**Rilpivirine Pharmacokinetics in Adults and in Adolescents aged 12 to <18 Years[1]**

| Parameter | Adults | Adolescents Aged 12 to <18 years |
|---|---|---|
| Dose | 25 mg once daily | 25 mg once daily |
| Number studied | 679 | 34 |
| **$AUC_{24h}$ (ng•h/mL)** | | |
| Mean ± Standard Deviation | 2,235 ± 851 | 2,424 ± 1,024 |
| Median (Range) | 2,096 (198–7,307) | 2,269 (417–5,166) |
| **$C_{0h}$ (ng/mL)** | | |
| Mean ± Standard Deviation | 79 ± 35 | 85 ± 40 |
| Median (Range) | 73 (2–288) | 79 (7–202) |

**Key to Acronyms:** AUC = area under the curve; $C_0$ = plasma concentration just prior to next dose;

In a PK study of youth aged 13 to 23 years receiving rilpivirine,[10] rilpivirine exposure was comparable to the results from PAINT in those receiving 25 mg rilpivirine without darunavir/ritonavir (DRV/r) and substantially higher in those receiving 25 mg rilpivirine with DRV/r (AUC = 6,740 ngxh/mL). No dose adjustments are currently recommended for adults when rilpivirine is used in DRV/r , where a similar 2- to 3-fold increase in rilpivirine exposure has been reported.[1]

***Toxicity***

In the PAINT study the observed adverse events (AEs) were similar to those reported in adults (e.g., somnolence, nausea, vomiting, abdominal pain, dizziness, headache). The incidence of depressive disorders was 19.4% (7/36) compared to 9% in the Phase III trials in adults. The incidence of grades 3 and 4 depressive disorders was 5.6% (2/36).[1]

Six of 30 (20%) adolescents 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 these results is not known but warrants further evaluation.[1]

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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 April 27, 2017; last reviewed April 27, 2017)

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**

- *[Evotaz]* Atazanavir 300 mg plus cobicistat 150 mg

**Capsules and powder packets are not interchangeable**.

## Dosing Recommendations

### Neonate Dose:

- Not approved for use in neonates and infants younger than 3 months. Atazanavir should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

### Pediatric Dose

*Powder Formulation:*[a]

- Powder formulation must be administered with ritonavir.
- Not approved for use in infants aged <3 months or weighing less than 5 kg.

### Infants and Children (Aged ≥3 Months; Weighing ≥5 kg):

**Atazanavir Powder**[a]

| Weight (kg) | Once-Daily Dose |
|---|---|
| 5 to <15 kg | Atazanavir 200 mg (4 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food |
| 15 to <25 kg[b] | Atazanavir 250 mg (5 packets) plus ritonavir 80 mg (1 mL oral solution), both once daily with food |

*Capsule Formulation:*[a]

- Not approved for use in children <6 years or <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 such as applesauce or 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 (<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 dosage of oral powder within 1 hour of preparation.
- Because atazanavir can prolong the ECG

**Children (Aged ≥6 Years; Weighing ≥15 kg):**

**Atazanavir Capsules[a]**

| Weight (kg) | Once-Daily Dose |
|---|---|
| <15 kg | Capsules not recommended |
| 15 to <20 kg | Atazanavir 150 mg plus ritonavir[c] 100 mg, both once daily with food |
| 20 to <40 kg[d] | Atazanavir 200 mg plus ritonavir[c] 100 mg, both once daily with food |
| ≥40 kg | Atazanavir 300 mg plus ritonavir[c] 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-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**

*Antiretroviral-Naive Patients:*

- Atazanavir 300 mg plus ritonavir 100 mg once daily with food.[e]
- Atazanavir 300 mg plus cobicistat[f] 150 mg, both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 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]).

*Antiretroviral-Experienced Patients:*

- Atazanavir 300 mg plus ritonavir 100 mg, both once daily with food.[e]
- Atazanavir 300 mg plus cobicistat[f] 150 mg,

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 Drug Interactions using 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 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 (PPIs) 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 PPIs 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).
- Dosing of atazanavir in patients with hepatic impairment: Atazanavir should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. Atazanavir should not be used in patients with severe hepatic impairment.
- Dosing of atazanavir in patients with renal

both once daily with food or as co-formulated Evotaz once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.

*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.[e]
- 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.[e]
- Atazanavir 300 mg plus cobicistat[f] 150 mg plus TDF 300 mg, all once daily with food. Cobicistat is currently not recommended for use in children aged <18 years, but is under investigation for children and youth aged 3 months to 18 years.
- Only boosted atazanavir should be used in combination with TDF because TDF decreases atazanavir exposure.

impairment: No dose adjustment is required for patients with renal impairment. However, atazanavir should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

[a] mg/kg dosing is higher for the powder packets than for the capsules. Bioavailability is higher for the capsules than for the powder when studied in adults.

[b] For a child who cannot swallow atazanavir capsules and who weighs ≥ 25 kg, 300 mg (6 packets) atazanavir powder plus ritonavir oral solution 100 mg, both once daily with food, may be used.

[c] Either ritonavir capsules or ritonavir oral solution can be used.

[d] Some experts would increase atazanavir to 300 mg at ≥35 kg to avoid under-dosing, especially when administered with TDF (see text for discussion).

[e] For adult patients who cannot swallow capsules, atazanavir oral powder is taken once daily with food at the same adult dosage as the capsules along with ritonavir.

[f] See 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 [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents] and [http://www.hiv-druginteractions.org/])

- *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. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme uridine diphosphate glucuronosyltransferase (UGT1A1). A patient’s medication profile should be carefully reviewed for potential drug interactions with atazanavir before the drug 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-naive 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. When atazanavir is administered with medications that alter gastric pH, dosage adjustment is indicated. Guidelines for dosing atazanavir with antacids, H2 receptor antagonists, and proton-pump inhibitors in adults are complex and can be found in the prescribing information brochure. No information is available on dosing atazanavir in children when the drug is co-administered with medications that alter gastric pH.
- Initiation of cobicistat, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving cobicistat may increase plasma concentration of these medications, which 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 CYP3A inducers may lead to lower exposure of cobicistat and atazanavir and loss of efficacy of atazanavir and possible resistance.[1] 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 (EKG). Abnormalities in atrioventricular (AV) conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild-to-moderate, but in rare cases includes life-threatening Stevens Johnson syndrome. Fat maldistribution and lipid abnormalities may be less common than with other PIs. However, 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 preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or hepatitis C are at increased risk).

### *Resistance*

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

### *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 in Clinical Trials:

- 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-naive adults.[2-5] In ACTG A5257, ATV/r was compared to darunavir/ritonavir (DRV/r) or raltegravir, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, ATV/r was discontinued more frequently than the other regimens due to toxicity, most often hyperbilirubinemia or gastrointestinal complaints.[6]
- P1020 enrolled 195 antiretroviral therapy (ART)-naive and ART-experienced patients with HIV infection aged 3 months to 21 years. Capsule and powder formulations and boosted and unboosted regimens were studied in this open-label study; targeted area under the curve (AUC)-directed 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 naive patients and 43.3% of the experienced patients had HIV viral loads ≤400 copies/mL.[7,8]
- Atazanavir in a powder formulation administered once daily boosted with liquid ritonavir was studied in infants and children aged ≥3 months and weighing ≥5 kg in 2 open-label clinical trials, PRINCE I and PRINCE II.[9,10] One hundred and thirty-four infants and children weighing between 5 and 35 kg were evaluated. Using a modified intent-to-treat analysis, overall proportions of antiretroviral (ARV)-naive and ARV-experienced patients with HIV RNA <50 copies/mL at Week 48 were 54% (28/452) and 50% (41/82), respectively. The median increase from baseline in absolute CD4 T lymphocyte (CD4) count (percent) at 48 weeks of therapy was 215 cells/mm$^3$ (6%) in ARV-naive patients and 133 cells/mm$^3$ (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$^2$ 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$^2$ per day of atazanavir capsule formulation to achieve PK targets.[8] Unboosted atazanavir at this dose was well tolerated in those aged <13 years who were able to swallow capsules.[11] Doses required for older adolescents were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily; adolescents aged >13 years required atazanavir dosing of 620 mg/m$^2$ per day.[8] 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 minimum plasma concentration ($C_{min}$) lower for the unboosted arms. Median doses of atazanavir in mg/m$^2$ 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.[12] Higher target trough concentrations may be required in PI-experienced patients.

**Summary of Atazanavir Dosing Information Obtained from IMPAACT/PACTG 1020A[8]**

| Age Range (Years) | ATV Given with RTV | ATV Median Dose (mg/m$^2$)[a] | ATV Median Dose (mg*) |
|---|---|---|---|
| 6–13 years | No | 509 | 475 |
| 6–13 years | Yes | 208 | 200 |
| >13 years | No | 620 | 900 |
| >13 years | Yes | 195 | 350 |

[a] 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:** AUC = area under the curve; ATV = atazanvir; PK = pharmacokinetic; RTV = ritonavir

In the report of the P1020A data, atazanavir satisfied PK criteria at a dose of 205 mg/m$^2$ in pediatric subjects when dosed with ritonavir.[1] However, given the available atazanavir capsule dose strengths, it is not possible to administer the exact mg dose equivalent to the body surface area-based dose. A study of a model-based approach using atazanavir concentration-time data from 3 adult studies and 1 pediatric study (P1020A) supports the use of the following weight-based ATV/r doses that are listed in the current FDA-approved product label for children aged ≥6 to <18 years:

- 150/100 mg (15 to <20 kg)
- 200/100 mg (20 to <40 kg)
- 300/100 mg (≥40 kg)[13]

The modeling used in the study does not assume 100% treatment adherence and has been shown to perform better than conventional modeling.[13] The authors acknowledge that ATV/r at 250/100 mg appeared to be a more appropriate dose than ATV/r at 200/100 mg for the 35 to <40 kg weight group; however, this dose is not achievable with current capsule dose strengths (150, 200, and 300 mg).[13] Some experts would increase atazanavir to 300 mg at ≥35 kg to avoid underdosing, especially when administered with TDF.

*Cobicistat as a Pharmacokinetic Enhancer*

No data are available on the use of cobicistat in pediatric patients.

*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$^2$ 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.[8]

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[9]
- PRINCE II: In pediatric patients aged 3 months to <11 years[10]

134 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 2 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)[a] versus Capsules in Young Adults[b] and Adults[a]**

| PK Parameters | Prince Trial[a] ATV/r<br>Dose 150/80 (mg)<br>Body Weight (kg) 5 to <10 | Prince Trial[a] ATV/r<br>Dose 200/80 (mg)<br>Body Weight (kg) 5 to <10 | Prince Trial[a] ATV/r<br>Dose 200/80 (mg)<br>Body Weight (kg) 10 to <15 | Prince Trial[a] ATV/r<br>Dose 250/80 (mg)<br>Body Weight (kg) 15 to <25 | Prince Trial[a] ATV/r<br>Dose 300/100 (mg)<br>Body Weight (kg) ≥25 to <35 | Young Adult Study[b] | Adult Study[a] |
|---|---|---|---|---|---|---|---|
| **AUC ng•h/mL**<br>Mean[c] (CV% or (95% CI) [n] | 32,503 (61%) [20] | 39,519 (54%) [10] | 50,305 (67%) [18] | 55,525 (46%) [31] | 44,329 (63%) [8] | 35,971 (30,853–41,898) [22] | 46,073 (66%) [10] |
| **C24 ng/mL**<br>Mean[c] (CV% or (95% CI) [n]) | 336 (76%) [20] | 550 (60%) [10] | 572 (111%) [18] | 678 (69%) [31] | 468 (104%) [8] | 578 (474–704) [22] | 636 (97%) [10] |

[a] Reyataz package insert[10]

[b] The young adults were also receiving TDF.[8]

[c] Means are geometric means.

**Key to Acronyms:** ATV/r = atazanavir/ritonavir; AUC = area under the curve; CI = confidence interval; CV = coefficient of variation

While the PK targets were met in these PK studies of atazanavir powder in all but the ATV/r 150/80 mg dose, 5 to <10 kg weight band, there were large coefficient of variation (CV)%, especially in the youngest patients.

*Transitioning from Powder to Capsules*

For children who reach a weight ≥25 kg while taking the powder, 300 mg (6 packets) atazanavir 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 is 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 ≥5.1 times the upper limit of normal.[11] Asymptomatic EKG abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in 1 patient, Grade 2 PR or HR changes in 9 patients, and Grade 3 PR prolongations in 3 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 2 NRTIs.[10]

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# Darunavir (DRV, Prezista) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Oral suspension:** 100 mg/mL

**Tablets *[Prezista]*:** 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 (boosting agent): ritonavir (children and adults) or cobicistat (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 ≤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 ≥3 years:*

- See table below for children aged ≥3 years who are antiretroviral **treatment-naive and treatment-experienced** with or without one or more darunavir resistance-associated mutations.

**Aged 3 to <12 Years and Weighing ≥10 kg**

| Weight (kg) | Dose (**Twice** daily with food)[a] |
|---|---|
| 10 to <11 kg[b] | Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL) |
| 11 to <12 kg[b] | Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL[c]) |
| 12 to <13 kg[b] | Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL[c]) |
| 13 to <14 kg[b] | Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL[c]) |
| 14 to <15 kg | Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL[c]) |
| 15 to <30 kg | Darunavir 375 mg (combination of tablets or 3.8 mL[d]) plus ritonavir 48 mg (0.6 mL[d]) |
| 30 to <40 kg | Darunavir 450 mg (combination of tablets or 4.6 mL[d]) plus ritonavir 100 mg (tablet or 1.25 mL[b]) |
| ≥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 one 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 depending on 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 ≥40 kg)[e] 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[f] 150 mg (tablet) or coformulated as Prezcobix **once daily with food**

**Adolescent (Weight ≥30 to <40 kg; Treatment-Experienced with at Least 1 Darunavir Resistance-Associated Mutation):**

- Darunavir 450 mg (combination of tablets) plus ritonavir 100 mg both **twice daily with food**

**Adolescent (Weight ≥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.

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.

Dosing in Patients with Renal Impairment:

- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min).

[a] Once-daily dosing is Food and Drug Administration-approved but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend it for children (see text under Frequency of Administration).

[b] Note that the dose in children weighing 10 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.

[c] Ritonavir 80 g/mL oral solution

[d] The 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

[e] Some Panel members recommend once daily darunavir 675 mg (combination of tablets) plus ritonavir 100 mg once daily for adolescents with body weight ≥30 to <40 kg, especially those ≥12 years of age.

[f] See cobicistat section for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.

***Drug Interactions*** (see also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents]() and [http://www.hiv-druginteractions.org/](http://www.hiv-druginteractions.org/))

- *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. Potential exists for multiple drug interactions when either ritonavir or cobicistat is used with darunavir. Co-administration of darunavir/ritonavir or darunavir/cobicistat 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. 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, crystalluria.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors such as hepatitis B or hepatitis C virus coinfection.

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see [http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10](http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10)) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see [http://hivdb.stanford.edu/DR/](http://hivdb.stanford.edu/DR/)).

***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-naive and treatment-experienced children aged 3 years and older.

*Efficacy in Clinical Trials*

- Data from the randomized, open-label, multicenter pediatric trial, which evaluated darunavir with ritonavir twice daily among 80 treatment-experienced children aged 6 to <18 years, demonstrated that 66% of patients had week 24 plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL.[1,2]
- In an international, multisite clinical trial (TMC114-TiDP29-C228) involving treatment-experienced children aged 3 to <6 years, 81% of children (out of 21) had viral load <50 copies/mL at week 48.[2,3]

***Pharmacokinetics and Dosing***

*Pharmacokinetics in Children Aged 3 to <6 Years*

Administration of twice-daily darunavir/ritonavir oral suspension in children aged 3 to <6 years and weighing 10 to <20 kg was conducted in 21 children who experienced failure of their previous ART regimen and had fewer than 3 darunavir resistance mutations on genotypic testing.[1-3] The darunavir area under the curve [$AUC_{(0–12h)}$], measured as a percent of the adult AUC value, was 128% overall: 140% in subjects weighing 10 to <15 kg and 122% in subjects weighing 15 to <20 kg.[1-3]

*Pharmacokinetics in Children Aged >6 Years*

Using darunavir tablets and ritonavir liquid or tablets, initial pediatric pharmacokinetic (PK) evaluation was based upon a Phase II randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 to <18 years and weighing ≥20 kg.[4] In Part I of the trial, a weight-adjusted dose of darunavir 9 to 15 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily, equivalent to the standard adult dose of darunavir/ritonavir 600/100 mg twice daily, resulted in inadequate drug exposure in the pediatric population studied with 24-hour AUC ($AUC_{24h}$) of 81% and pre-dose concentration ($C_{0h}$) 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 was the dose selected for Part II of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 to 19 mg/kg and ritonavir 1.5 to 2.5 mg/kg twice daily. This resulted in darunavir $AUC_{24h}$ of 123.3 mcg*h/mL (range 71.9–201.5) and $C_{0h}$ of 3,693 ng/mL (range 1,842–7,191), 102% and 114% of the respective PK values in adults. Doses were given twice daily and were stratified by body weight bands of 20 to <30 kg and 30 to <40 kg. Based on the findings in the safety and efficacy portion of the study, current weight-band doses of twice-daily darunavir/ritonavir for treatment-experienced pediatric patients with weight >20 to <40 kg were selected (see Table A).

**Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Backbone (Children Aged 3–18 Years and Adults Aged >18 Years)**

| Population | N | Dose of DRV/RTV | $AUC_{12h}$ (mcg*h/mL) Median[a] | $C_{0h}$ (ng/mL) Median[a] |
|---|---|---|---|---|
| 10 to <15 kg[a] | 13 | 20/3 mg/kg | 66.0 | 3,533 |
| 10 to <15 kg[a] | 4 | 25/3 mg/kg | 116.0 | 8,522 |
| 15 to <20 kg[a] | 11 | 20/3 mg/kg | 54.2 | 3,387 |
| 15 to <20 kg[a] | 14 | 25/3 mg/kg | 68.6 | 4,365 |
| Aged 6 to <12 years[b] | 24 | Weight bands[b] | 56.4 | 3,354 |
| Aged 12 to <18 years[b] | 50 | Weight bands[b] | 66.4 | 4,059 |
| Adults aged >18 years (3 studies)[c] | 285/278/119 | 600/100 mg | 54.7–61.7 | 3,197–3,539 |

[a] Source: Food and Drug Administration. FDA pharmacokinetics review. 2011. Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf.

[b] Weight band dosing was with darunavir/ritonavir at doses of 375/50 mg twice daily for body weight 20 to <30 kg, 450/60 mg twice daily for 30 to <40 kg, and 600/100 mg twice daily for ≥40 kg. Data from FDA pharmacokinetics review 2008. Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf.

[c] Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017lbledt.pdf.

**Key to Acronyms:** AUC = area under the curve; $C_{0h}$ = pre-dose concentration; DRV = darunavir; RTV = ritonavir

***Dosing***

*Pharmacokinetic Enhancers*

Darunavir should not be used without a PK enhancer (boosting agent): ritonavir (children and adults) or cobicistat (adults only).

A study in 19 Thai children used ritonavir 100-mg capsule twice daily as the boosting dose with twice-daily darunavir doses of 375 mg (body weight 20 to <30 kg), 450 mg (body weight 30–40 kg), and 600 mg twice daily (body weight ≥40 kg).[5] 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.[4,5] The tolerability and PK data from this small study support the higher doses of ritonavir boosting with 100-mg capsule or tablet in children with body weight ≥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 who weigh less than 20 kg.

Data on dosing of cobicistat with darunavir are available in adult patients only.[6] Data on a fixed-dose combination of 800/150 mg darunavir/cobicistat once daily showed comparable bioavailability to that obtained with 800/100 mg of darunavir/ritonavir once daily.[7]

*Frequency of Administration*

In February 2013, the FDA approved the use of once-daily darunavir for treatment-naive children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). To derive once-daily pediatric dosing recommendations for younger pediatric subjects aged 3 to <12 years weighing 10 to <40 kg, population PK modeling and simulation were used.[2,8] A dedicated pediatric trial evaluating once-daily darunavir with ritonavir dosing in children aged 6 to <12 years was not conducted. No efficacy data have been obtained regarding use of once-daily darunavir with ritonavir in treatment-naive or treatment-experienced children aged <12 years. **Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV generally recommends dosing darunavir with ritonavir twice daily in children aged ≥3 years to <12 years** (see Once-Daily Dosing section). The Panel recommends that once-daily darunavir with ritonavir be used only in treatment-naive and treatment-experienced adolescents weighing ≥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 (see Therapeutic Drug Monitoring) and close monitoring of viral load.

FDA approval was based on results from 2 small pediatric trials: TMC114-C230 evaluating once-daily dosing in treatment-naive adolescents aged 12 to 18 years and weighing ≥40 kg (see below) and the TMC114-C228 sub-trial evaluating once-daily dosing in treatment-experienced children aged 3 to <6 years (see below).[8-10]

**Table B. FDA-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg who are ART-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations**

| **Weight** (kg) | **Dose** (Once daily with food) |
|---|---|
| 10 to <11 kg[a] | DRV 350 mg (3.6 mL[b]) plus RTV 64 mg (0.8 mL[c]) |
| 11 to <12 kg[a] | DRV 385 mg (4 mL[b]) plus RTV 64 mg (0.8 mL[c]) |
| 12 to <13 kg[a] | DRV 420 mg (4.2 mL) plus RTV 80 mg (1 mL[c]) |
| 13 to <14 kg[a] | DRV 455 mg (4.6 mL[b]) plus RTV 80 mg (1 mL[c]) |
| 14 to <15 kg | DRV 490 mg (5 mL[b]) plus RTV 80 mg (1 mL[c]) |
| 15 to <30 kg | DRV 600 mg (tablet or combination of tablets or 6 mL) plus RTV 100 mg (tablet or 1.25 mL[c]) |
| 30 to <40 kg | DRV 675 mg (combination of tablets or 6.8 mL[b,d]) plus RTV 100 mg (tablet or 1.25 mL[c]) |
| ≥40 kg | DRV 800 mg (tablet or combination of tablets or 8 mL[d]) plus RTV 100 mg (tablet or 1.25 mL[c]) |

[a] The dose in children weighing 10 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.

[b] RTV 80 mg/mL oral solution.

[c] The 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.

[d] The 6.8-mL and 8-mL DRV doses can be taken as two administrations (3.4 mL and 4 mL, respectively) with the included oral dosing syringe, or as one syringe when provided by pharmacy or medical office.

**Note:** The Panel generally recommends dosing darunavir with ritonavir twice daily in children aged ≥3 years to <12 years

**Key to Acronyms:** DRV = darunavir; RTV = ritonavir

*Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg*

As part of the TMC114-C228 trial that evaluated twice-daily dosing in treatment-experienced children aged 3 to <12 years, once-daily dosing of darunavir for 2 weeks with PK evaluation was conducted as a sub-study, after which the participants switched back to the twice-daily regimen.[8,11] The darunavir/ritonavir 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 darunavir/ritonavir 600 mg/100 mg once daily for children weighing ≥15 kg.[8,11] 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 darunavir with ritonavir in children aged 3 to <12 years. Despite the FDA dosing guidelines and because of the small set of data used for modeling and lack of efficacy data on once-daily darunavir with ritonavir in treatment-naive or treatment-experienced children aged <12 years, **the Panel generally recommends dosing darunavir with ritonavir twice daily in children aged ≥3 years to <12 years**.

**Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone[11]**

| PK Parameter | Once-Daily Darunavir Sub-Study (n = 10) 3–6 years | Adult Study (n = 335) |
|---|---|---|
| DRV $AUC_{24h}$ geometric mean, ng*h/mL (SD) | 115 (40.6) | 89.7 (27.0) |
| DRV $C_{0h}$ geometric mean, ng/mL (SD) | 3,029 (1,715) | 2,027 (1,168) |

**Key to Acronyms:** AUC = area under the curve; $C_{0h}$ = pre-dose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

*Once-Daily Administration in Adolescents Aged ≥12 and Weighing ≥40 kg*

A sub-study of once-daily dosing of darunavir 800 mg with ritonavir 100 mg in 12 treatment-naive 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).[9] 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.[10] Interestingly, no relationship was observed between darunavir $AUC_{24h}$ and $C_{0h}$ and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those 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 (14–23 years).[12] 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.[13]

**Table D. Darunavir Pharmacokinetics with Once-Daily Administration (Adolescents Aged ≥12 Years and Adults Aged >18 Years)**

| Population | N | Dose of DRV/RTV | $AUC_{24h}$[a] (mcg*h/mL) median | $C_{0h}$ (ng/mL) median |
|---|---|---|---|---|
| Aged 12–17 years (mean 14.6)[9] | 12 | 800/100 mg | 86.7 | 2,141 |
| Aged 14–23 years (mean 19.5)[12] | 24 | 800/100 mg | 69.5 | 1,300 |
| Adults aged >18 years (2 studies)[a] | 335/280 | 800/100 mg | 87.8–87.9 | 1,896–2,041 |

[a] Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017lbledt.pdf.

**Key to Acronyms:** $AUC_{24h}$ = 24-hour area under the curve; $C_{0h}$ = pre-dose concentration; DRV = 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.[10,14]

*Co-Administration with Other Antiretrovirals*

**Nucleotide Reverse Transcriptase Inhibitor**

When darunavir/ritonavir twice daily 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.[15] No dose adjustment is recommended for use of the combination of darunavir/ritonavir with either of these drugs, but caution is advised and therapeutic drug monitoring (TDM) may be potentially useful.

**Non-Nucleoside Reverse Transcriptase Inhibitors**

Recent data from the IMPAACT protocol P1058A report that the co-administration of once daily darunavir/ritonavir 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.[16] When darunavir/ritonavir was co-administered with etravirine twice daily in pediatric patients, target concentrations for both darunavir and etravirine were achieved.[17] When co-administered once daily, darunavir PKs have not been affected by co-administration of rilpivirine in adolescents and young adults.[18] Darunavir/ritonavir co-administration increased rilpivirine exposure 2-to 3-fold, indicating that drug-related adverse effects should be closely monitored.

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# Fosamprenavir (FPV, Lexiva) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 HIV-Infected Children (the Panel) because of low exposures (see text below).
- Boosted fosamprenavir (with ritonavir) is FDA-approved for ARV-naive infants ≥4 weeks and for treatment-experienced infants ≥6 months; however, the Panel does not recommend use in infants younger than 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.

**Once-daily dosing is not recommended for any pediatric patient.**

### Aged ≥6 Months to 18 Years:

**Twice-Daily Dosage Regimens by Weight for Pediatric Patients ≥6 Months Using Lexiva Oral Suspension with Ritonavir**

| Weight | Dose<br>Fosamprenavir Plus Ritonavir<br>Both twice daily[a] with food |
|---|---|
| <11 kg | fosamprenavir 45 mg/kg/dose plus ritonavir 7 mg/kg/dose |
| 11 kg to <15 kg | fosamprenavir 30 mg/kg/dose plus ritonavir 3 mg/kg/dose |
| 15 kg to <20 kg | fosamprenavir 23 mg/kg/dose plus ritonavir 3 mg/kg/dose |
| ≥20 kg | fosamprenavir 18 mg/kg/dose plus ritonavir 3 mg/kg/dose |

[a] Not to exceed the adult dose of fosamprenavir 700 mg plus ritonavir 100 mg twice daily.

## Selected Adverse Events

- Diarrhea, nausea, vomiting
- Skin rash (Fosamprenavir has a sulfonamide moiety. Stevens-Johnson syndrome and erythema multiforme have been reported.)
- Headache
- Hyperlipidemia, hyperglycemia
- Nephrolithiasis
- Transaminase elevation
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia

## Special Instructions

- Fosamprenavir tablets with ritonavir should be taken with food. Children should take the suspension with food.
- Patients taking antacids or buffered formulations of didanosine should take fosamprenavir at least 1 hour before or after antacid or didanosine 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 P450 3A4 (CYP3A4) inhibitor, inducer, and substrate.

**Note:** When administered with ritonavir, the adult regimen of 700 mg fosamprenavir tablets plus 100 mg ritonavir, both given twice daily, can be used in patients weighing ≥39 kg. Ritonavir tablets can be used in patients weighing ≥33 kg.

**Adolescent and Adult (Aged >18 Years) Dose:**

- Dosing regimen depends on whether the patient is ARV naive or ARV experienced.

*ARV-Naive Patients*

Boosted with Ritonavir, Twice-Daily Regimen:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.

Boosted with Ritonavir, Once-Daily Regimen:

- Fosamprenavir 1400 mg plus ritonavir 100–200 mg, both once daily.

*Protease Inhibitor (PI)-Experienced Patients:*

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily.
- **Note:** Once-daily administration of fosamprenavir plus ritonavir is not recommended.

*Fosamprenavir in Combination with Efavirenz (Adult):*

- Only fosamprenavir boosted with ritonavir should be used in combination with efavirenz.

Twice-Daily Regimen:

- Fosamprenavir 700 mg plus ritonavir 100 mg, both twice daily plus efavirenz 600 mg once daily.

PI-Naive Patients Only, Once-Daily Regimen:

- Fosamprenavir 1400 mg plus ritonavir 300 mg plus efavirenz 600 mg, all once daily.

- Dosing in patients with hepatic impairment: Dosage adjustment is recommended. Please refer to the package insert.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- Fosamprenavir has the potential for multiple 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 in clinical trials of fosamprenavir with ritonavir (20% to 36% vs. 10%, respectively) and in trials of fosamprenavir without ritonavir (60% vs. 16%, respectively). Neutropenia was also more common in children across all the trials (15% vs. 3%, respectively).[1]

### Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

### Pediatric Use

*Approval*

Fosamprenavir is Food and Drug Administration (FDA)-approved for use in children as young as age 4 weeks, but The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends use only in children aged 6 months or older. While unboosted fosamprenavir has been approved by the FDA for antiretroviral-naive children aged 2 to 5 years, the Panel does not recommend unboosted fosamprenavir for this—or any other—age group because of low exposures and because unboosted fosamprenavir may select for mutations associated with resistance to darunavir.[2]

### Efficacy and Pharmacokinetics

Dosing recommendations for fosamprenavir are based on three pediatric studies that enrolled over 200 children aged 4 weeks to 18 years. In two open-label trials in both treatment-experienced and treatment-naive children aged 2 to 18 years,[3,4] fosamprenavir was well-tolerated and effective in suppressing viral load and increasing CD4 T lymphocyte count. However, data were insufficient to support a once-daily dosing regimen of ritonavir-boosted fosamprenavir in children; therefore, once-daily dosing is not recommended for pediatric patients.

*Pharmacokinetics in Infants*

In a study of infants, higher doses of both fosamprenavir and ritonavir were used in treatment-naive infants as young as 4 weeks and in treatment-experienced infants as young as 6 months.[1,5] Exposures in those younger than 6 months were much lower than those achieved in older children and adults and comparable to those seen with unboosted fosamprenavir. 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 younger than 6 months.

| Population | Dose | $AUC_{0\text{-}24}$ (mcg*hr/mL) Except Where Noted | $C_{min}$ (mcg/mL) |
|---|---|---|---|
| **Infants <6 Months** | 45 mg fosamprenavir/10 mg ritonavir per kg twice daily | 26.6[a] | 0.86 |
| **Children Aged 2 to <6 Years** | 30 mg fosamprenavir per kg twice daily (no ritonavir) | 22.3[a] | 0.513 |
| **Children Weighing <11 kg** | 45 mg fosamprenavir/7 mg ritonavir per kg twice daily | 57.3 | 1.65 |
| **Children Weighing 15 to <20 kg** | 23 mg fosamprenavir/3 mg ritonavir per kg twice daily | 121.0 | 3.56 |
| **Children Weighing ≥20 kg** | 18 mg fosamprenavir/3 mg ritonavir per kg twice daily (maximum 700/100 mg) | 72.3–97.9 | 1.98–2.54 |
| **Adults** | 1400 mg fosamprenavir twice daily (no ritonavir) | 33 | 0.35 |
| **Adults** | 1400 mg fosamprenavir/100–200 mg ritonavir once daily | 66.4–69.4 | 0.86–1.45 |
| **Adults** | 700 mg fosamprenavir/100 mg ritonavir twice daily | 79.2 | 2.12 |

[a] $AUC_{0\text{-}12}$ (mcg*hr/mL)

**Note:** Dose for those weighing 11 to <15 kg is based on population pharmacokinetic studies; therefore, area under the curve and $C_{min}$ are not available.

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# Indinavir (IDV, Crixivan) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Capsules:** 100 mg, 200 mg, and 400 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Not approved for use in neonates/infants.
- Should not be administered to neonates because of the risks associated with hyperbilirubinemia (kernicterus).

### Pediatric Dose:

- Not approved for use in children.
- A range of indinavir doses (234–500 mg/$m^2$ body surface area) boosted with low-dose ritonavir has been studied in children (see text below).

### Adolescent and Adult Dose:

- 800 mg indinavir plus 100 or 200 mg ritonavir every 12 hours

## 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 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).
- If co-administered with didanosine, give indinavir and didanosine ≥1 hour apart on an empty stomach.
- Indinavir capsules are sensitive to moisture; store at room temperature (59–86º F) in original container with desiccant.

## Metabolism/Elimination

- Cytochrome P450 3A4 (CYP3A4) inhibitor and substrate
- Dosing in patients with hepatic impairment: Decreased dosage should be used 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 [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents] and http://www.hiv-druginteractions.org/)

- *Metabolism:* CYP3A4 is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.
- 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%).[1] 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***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.[2] Indinavir is not recommended by Panel members for use in children 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 infection. An unboosted indinavir dose of 500 to 600 $mg/m^2$ body surface area given every 8 hours results in peak blood concentrations and area under the curve slightly higher than those in adults, but considerably lower trough concentrations. A significant proportion of children have trough indinavir concentrations less than the 0.1 mg/L value associated with virologic efficacy in adults.[3-6] Studies in small groups of children of a range of indinavir/ritonavir doses have shown that indinavir 500 $mg/m^2$ body surface area plus ritonavir 100 $mg/m^2$ body surface area twice daily is probably too high,[7] that indinavir 234 to 250 $mg/m^2$ body surface area plus low-dose ritonavir twice daily is too low,[8,9] and that indinavir 400 $mg/m^2$ body surface area plus ritonavir 100 to 125 $mg/m^2$ body surface area twice daily results in exposures approximating those seen with 800 mg indinavir/100 mg ritonavir twice daily in adults, albeit with considerable inter-individual variability and high rates of toxicity.[9-11]

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# Lopinavir/Ritonavir (LPV/r, Kaletra) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Pediatric Oral Solution:** 80 mg/20 mg LPV/r per mL (contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume)

**Film-Coated Tablets:** 100 mg/25 mg LPV/r, 200 mg/50 mg LPV/r

## Dosing Recommendations

### Neonatal Dose (<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 because of potential toxicities.

### Dosing for Individuals not Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir

*Infant Dose (14 Days–12 Months):*

- Once-daily dosing **is not recommended**.
- 300 mg/75 mg lopinavir/ritonavir per $m^2$ of body surface area twice daily (approximates 16 mg/4 mg lopinavir/ritonavir 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 $m^2$ dose).

*Pediatric Dose (>12 Months to 18 Years):*

- Once-daily dosing **is not recommended**.
- 300 mg/75 mg lopinavir/ritonavir per $m^2$ of body surface area per dose twice daily (maximum dose 400 mg/100 mg lopinavir/ritonavir twice daily except as noted below). For patients with body weight <15 kg, this approximates 13 mg/3.25 mg lopinavir/ritonavir per kg body weight twice daily; and for patients with body weight ≥15 to 45 kg this dose approximates 11 mg/2.75 mg lopinavir/ritonavir per kg body weight twice daily. This dose is routinely used by many clinicians and is the preferred dose for treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility (see text below).

## 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

- Lopinavir/ritonavir tablets can be administered without regard to food; administration with or after meals may enhance GI tolerability.
- Lopinavir/ritonavir tablets must be swallowed whole. Do not crush or split tablets.
- Lopinavir/ritonavir oral solution should be administered with food because a high-fat meal increases absorption.
- The poor palatability of lopinavir/ritonavir oral solution is difficult to mask with flavorings or foods (see Pediatric Use).
- Lopinavir/ritonavir oral solution can be kept at room temperature up to 77° F (25° C) if used within 2 months. If kept refrigerated (2° to 8° C or 36° to 46° F) lopinavir/ritonavir oral solution remains stable until the expiration date printed on the label.
- Once-daily dosing is not recommended because of considerable variability in plasma concentrations in children aged <18 years and higher incidence of diarrhea.
- Use of lopinavir/ritonavir once daily is specifically contraindicated if three or more of

- 230 mg/57.5 mg lopinavir/ritonavir per $m^2$ of body surface area per dose twice daily can be used in antiretroviral (ARV)-naive patients aged >1 year. For patients <15 kg, this dose approximates 12 mg/3 mg lopinavir/ritonavir per kg body weight given twice daily and for patients ≥15 kg to 40 kg, this dose approximates 10 mg/2.5 mg lopinavir/ritonavir per kg body weight given twice daily. This dose **should not be used** in treatment-experienced patients who could harbor virus with decreased lopinavir susceptibility.

**Weight-Band Dosing for 100 mg/25 mg Lopinavir/Ritonavir Pediatric Tablets for Children/Adolescents**

| | Recommended Number of 100-mg/25-mg Lopinavir/Ritonavir Tablets Given Twice Daily | |
|---|---|---|
| **Dosing Target** | 300 mg/$m^2$/dose given twice daily | 230 mg/$m^2$/dose given twice daily |
| **Body Weight (kg)** | | |
| **15 to 20 kg** | 2 | 2 |
| **>20 to 25 kg** | 3 | 2 |
| **>25 to 30 kg** | 3 | 3 |
| **>30 to 35 kg** | 4[a] | 3 |
| **>35 to 45 kg** | 4[a] | 4[a] |
| **>45 kg** | 4[a] or 5[b] | 4[a] |

[a] Four of the 100 mg/25 mg lopinavir/ritonavir tablets can be substituted with 2 tablets each containing 200 mg/50 mg lopinavir/ritonavir in children capable of swallowing a larger tablet.

[b] In patients receiving concomitant nevirapine, efavirenz, fosamprenavir, or nelfinavir, for body weight >45 kg, the Food and Drug Administration (FDA)-approved adult dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing.

*Adult Dose (>18 Years):*

- 800 mg/200 mg lopinavir/ritonavir once daily, **or**
- 400 mg/100 mg lopinavir/ritonavir 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 Instructions for list).

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—because higher lopinavir trough concentrations may be required to suppress resistant virus.

## Metabolism/Elimination

- Cytochrome P (CYP) 3A4 inhibitor and substrate.
- Dosing of lopinavir/ritonavir in patients with hepatic impairment: Lopinavir/ritonavir is primarily metabolized by the liver. Caution should be used 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 lopinavir/ritonavir, 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.

**In Patients with Three or more Lopinavir-Associated Mutations (see Special Instructions for list):**

- 400 mg/100 mg lopinavir/ritonavir twice daily.

**Dosing for Individuals Receiving Concomitant Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir:**

**Note:** These drugs induce lopinavir metabolism and reduce lopinavir plasma levels; increased lopinavir/ritonavir dosing is required with concomitant administration of these drugs.

- Once-daily dosing should **not** be used.

*Pediatric Dose (>12 Months to 18 Years):*

- 300 mg/75 mg lopinavir/ritonavir per $m^2$ of body surface area per dose twice daily. See table for weight-band dosing when using tablets.

*Adult Dose (>18 Years):*

- FDA-approved dose is 500 mg/125 mg lopinavir/ritonavir twice daily, given as a combination of 2 tablets of 200/50 mg lopinavir/ritonavir and 1 tablet of 100 mg/25 mg lopinavir/ritonavir. Alternatively, 3 tablets of 200/50 mg lopinavir/ritonavir can be used for ease of dosing. Once-daily dosing should **not** be used.

**Lopinavir/Ritonavir in Combination with Saquinavir Hard-Gel Capsules (Invirase) or in Combination with Maraviroc:**

- Saquinavir and maraviroc doses may need modification (see the Saquinavir and Maraviroc sections for more information).

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://hivdb.stanford.edu/DR/)

- *Metabolism:* CYP450 3A4 (CYP3A4) is the major enzyme responsible for metabolism. There is potential for multiple drug interactions.

Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with lopinavir/ritonavir. In patients treated with lopinavir/ritonavir, 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 dosage adjustments or regimen change.

***Major Toxicities***

- *More common:* Diarrhea, headache, asthenia, nausea and vomiting, rash, and hyperlipidemia, especially hypertriglyceridemia,[1] possibly more pronounced in girls than boys.[2] In adults, lopinavir/ritonavir is associated with diarrhea, insulin resistance, and hyperlipidemia. These adverse events may be exacerbated by the higher dose of ritonavir used for boosting with lopinavir (200 mg) compared to 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:* Lopinavir/ritonavir **should not be used** in 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,[3] life-threatening bradyarrhythmias and cardiac dysfunction (including complete atrioventricular block, bradycardia, and cardiomyopathy),[4-6] and 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%.[6] Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported in term newborns treated at birth with lopinavir/ritonavir.[3]

### Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

### Pediatric Use

*Approval*

Lopinavir/ritonavir is Food and Drug Administration (FDA)-approved for use in children. Ritonavir acts as a pharmacokinetic (PK) enhancer by inhibiting the metabolism of lopinavir and thereby increasing the plasma concentration of lopinavir.

*Efficacy*

In clinical trials of treatment-naive adults, regimens containing LPV/r plus two NRTIs have been demonstrated to be comparable to a variety of other regimens including atazanavir, darunavir (at 48 weeks), fosamprenavir, saquinavir/ritonavir, and efavirenz, superior to nelfinavir, and inferior to darunavir (at 192 weeks).[7-15]

LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and low toxicity.[16-23]

### Pharmacokinetics

*General Considerations*

Children have lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The directly scaled dose approximation of the adult dose in children is calculated by dividing the adult dose by the usual adult body surface area of 1.73 $m^2$. For the adult dose of 400/100 mg lopinavir/ritonavir, the appropriate pediatric dose would be approximately 230/57.5 mg lopinavir/ritonavir per $m^2$. 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 similar $C_{trough}$ 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[18,23,24] are compared to those in older children[16] and adults[25] in the table below.

**Pharmacokinetics of Lopinavir/Ritonavir by Age**

| | Adults[25] | Children[16] | Children[16] | Infants[a] at 12 Months[23] | Infants 6 weeks–6 months[18] | Infants <6 weeks[24] |
|---|---|---|---|---|---|---|
| **N** | 19 | 12 | 15 | 20 | 18 | 9 |
| **Dose LPV** | 400 mg | 230 mg/m$^2$ | 300 mg/m$^2$ | 300 mg/m$^2$ | 300 mg/m$^2$ | 300 mg/m$^2$ |
| **AUC mcg-hr/mL** | 92.6 | 72.6 | 116.0 | 101.0 | 74.5 | 43.4 |
| **$C_{max}$ mcg/mL** | 9.8 | 8.2 | 12.5 | 12.1 | 9.4 | 5.2 |
| **$C_{trough}$ mcg/mL** | 7.1 | 4.7 | 7.9 | 4.9 | 2.7 | 2.5 |
| **$C_{min}$ mcg/mL** | 5.5 | 3.4 | 6.5 | 3.8 | 2.0 | 1.4 |

[a] Data generated in study 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[26] and with clearance slowing by age 2.3 years.[27] A study from the UK and Ireland in children ages 5.6 to 12.8 years at the time of lopinavir/ritonavir initiation that compared outcomes in children treated with 230 mg/m$^2$/dose versus 300 mg/m$^2$/dose suggests that the higher doses were associated with improved long-term viral load suppression.[28]

## Pharmacokinetics and Dosing

*12 Months to 12 Years (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

Lower trough concentrations have been observed in children receiving 230 mg/57.5 mg lopinavir/ritonavir per m$^2$ of body surface area when compared to 300 mg/75 mg lopinavir/ritonavir per m$^2$ of body surface area per dose twice daily (see table).[16] Therefore, some clinicians choose to initiate therapy in children aged 12 months to 12 years using 300 mg/75 mg lopinavir/ritonavir per m$^2$ of body surface area per dose twice daily (when given without nevirapine, efavirenz, fosamprenavir, or nelfinavir) rather than the FDA-recommended 230 mg/57.5 mg lopinavir/ritonavir per m$^2$ of body surface area per dose twice daily.

For infants receiving 300 mg/75 mg lopinavir/ritonavir per m$^2$ of body surface area per dose twice daily, immediate dose reduction at age 12 months is not recommended; many practitioners would allow patients to "grow into" the 230 mg/57.5 mg lopinavir/ritonavir per m$^2$ of body surface area per dose twice daily dosage as they gain weight over time. Some would continue the infant dose (300 mg/m$^2$ of body surface area per dose twice daily) while on lopinavir/ritonavir liquid formulation.

*Younger Than 6 Weeks to 12 Months (Without Concurrent Nevirapine, Efavirenz, Fosamprenavir, or Nelfinavir)*

The PK of the oral solution at approximately 300 mg/75 mg lopinavir/ritonavir per m$^2$ body surface area per dose twice daily was evaluated in infants younger than age 6 weeks[24] and infants aged 6 weeks to 6 months.[18] Even at this higher dose, pre-dose ($C_{trough}$) levels were highly variable but were lower in infants than in children older than age 6 months and were lowest in the youngest infants aged 6 weeks or younger compared with those aged 6 weeks to 6 months. By age 12 months, lopinavir area under the curve (AUC) was similar to that found in older children.[23] 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$^2$ body surface area in older children and adolescents,[19] some practitioners anticipate rapid infant growth and prescribe doses somewhat higher than the 300 mg/m$^2$ 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 $C_{trough}$ 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 230 mg/57.5 mg lopinavir/ritonavir per $m^2$ body surface area per dose twice daily plus nevirapine, the mean lopinavir $C_{trough}$ was 3.77 ± 3.57 mcg/mL.[16] Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of lopinavir/ritonavir, but the variability in concentration is much higher in children than in adults.[16,29] In a study of 15 children with HIV aged 5.7 to 16.3 years treated with the combination of 300 mg/75 mg lopinavir/ritonavir per $m^2$ body surface area per dose twice daily plus efavirenz 14 mg/kg body weight per dose once daily there was a 34-fold inter-individual variation in lopinavir trough concentrations, and 5 of 15 (33%) children had lopinavir 12-hour trough concentrations less than 1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV.[30] A PK study in 20 children aged 10 to 16 years treated with the combination of lopinavir/ritonavir 300 mg/75 mg per $m^2$ body surface area twice daily plus efavirenz 350 mg/$m^2$ body surface area once daily showed only 1 (6.6%) patient with sub-therapeutic lopinavir trough concentrations,[31] perhaps because of the use of a lower efavirenz dose of approximately 11 mg/kg body weight,[31] compared with efavirenz 14 mg/kg body weight in the Bergshoeff trial.[30]

## Dosing

### *Once Daily*

Once-daily dosing of lopinavir/ritonavir 800 mg/200 mg administered as a single daily dose is FDA-approved for treatment of HIV in therapy-naive adults older than age 18 years. However, once-daily administration **cannot be recommended for use in children in the absence of therapeutic drug monitoring (TDM)**. There is high inter-individual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus as demonstrated in studies of antiretroviral (ARV)-naive children and adolescents.[32-35] Compared with the soft-gel formulation of lopinavir/ritonavir, the tablet formulation has lower variability in trough levels.[35,36] An international, randomized, open-label trial designed to demonstrate noninferiority in viral suppression between once daily vs. twice daily LPV/r dosing in children (median [IQR] age of 11 [9–14] years) was unsuccessful, and more children on once daily dosing had viral load ≥50 copies/ml within 48 weeks.[37]

### *Dosing and Its Relation to Efficacy*

Lopinavir/ritonavir is effective in treatment-experienced patients with severe immune suppression,[38,39] although patients with greater prior exposure to ARVs may have slower reductions in viral load to undetectable concentrations[39,40] and less robust response in CD4 T lymphocyte (CD4) percentage.[41] Twice daily doses of lopinavir used in this cohort were 230 to 300 mg/$m^2$ body surface area in 39% of patients, 300 to 400 mg/$m^2$ body surface area in 35%, and greater than 400 mg/$m^2$ body surface area per dose in 4%.[41]

More important than viral resistance to lopinavir is the relationship of the drug exposure (trough plasma concentration measured just before a dose, or $C_{trough}$) to the susceptibility of the HIV-1 isolate ($EC_{50}$). The ratio of $C_{trough}$ to $EC_{50}$ is called the inhibitory quotient (IQ), and in both adults and children treated with lopinavir/ritonavir, viral load reduction is more closely associated with IQ than with either the $C_{trough}$ or $EC_{50}$ alone.[42-44] A study of the practical application of the IQ to guide therapy using higher doses of lopinavir/ritonavir in children and adolescents to reach a target IQ of 15 showed the safety and tolerability of doses of 400 mg/100 mg lopinavir/ritonavir per $m^2$ body surface area per dose twice daily (without fosamprenavir, nelfinavir, nevirapine, or efavirenz) and 480 mg/120 mg lopinavir/ritonavir per $m^2$ body surface area per dose twice daily (with nevirapine or efavirenz).[19] Results of a modeling study suggest that standard doses of lopinavir/ritonavir may be inadequate for treatment-experienced children and suggest the potential utility of TDM when lopinavir/ritonavir is used in children previously treated with protease inhibitors.[45]

## Formulations

### *Palatability*

The poor palatability of the lopinavir/ritonavir 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, chocolate syrup, or peanut butter, for example, or by having the pharmacist flavor the solution prior to dispensing, are examples of interventions that may improve tolerability. Alternative pediatric formulations are currently being developed.[46,47]

*Do Not Use Crushed Tablets*

Lopinavir/ritonavir 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.[48] In a PK study using a generic adult formulation of lopinavir/ritonavir manufactured in Thailand, 21 of 54 children were administered cut (not crushed) pills and had adequate lopinavir $C_{trough}$ measurements.[36]

**Toxicity**

*Weight Gain*

Compared with children treated with NNRTI-based regimens, those treated with lopinavir/ritonavir may have less robust weight gain and smaller increases in CD4 percentage.[21,49-51] The poor weight gain associated with lopinavir/ritonavir is not understood, but may be related to aversion to the taste of the liquid formulation or decreased appetite.

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# Nelfinavir (NFV, Viracept) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Tablets:** 250 mg and 625 mg

## Dosing Recommendations

### Neonate/Infant Dose:

- Nelfinavir should not be used for treatment in children aged <2 years.

### Pediatric Dose (Aged 2–13 Years):

- 45–55 mg/kg twice daily

### Adolescent and Adult Dose:

- 1250 mg (five 250-mg tablets or two 625-mg tablets) twice daily
- Some adolescents require higher doses than adults to achieve equivalent drug exposures. Consider using therapeutic drug monitoring to guide appropriate dosing.

## Selected Adverse Events

- Diarrhea
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Possible increase in bleeding episodes in patients with hemophilia

## 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, patients should 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

- CYP2C19 and 3A4 substrate
- Metabolized to active M8 metabolite
- CYP3A4 inhibitor

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Cytochrome P (CYP) 2C19 and 3A4 substrate. Metabolized to active M8 metabolite. CYP3A4 inhibitor. However, 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):* Exacerbation of chronic liver disease, fat redistribution.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevations in transaminases.

### *Resistance*

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

### *Pediatric Use*

*Approval*

Nelfinavir is a protease inhibitor (PI) approved for use in combination with 2 nucleoside reverse transcriptase inhibitors in children 2 to 13 years of age. Nelfinavir is not recommended for treatment of children aged <2 years.

*Efficacy in Pediatric Clinical Trials*

Nelfinavir in combination with other antiretroviral drugs has been extensively studied in children with HIV infection.[1-8] In randomized trials of children aged 2 to 13 years receiving nelfinavir as part of triple antiretroviral therapy (ART), 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 younger than age 2 years than in older children.[6,8,9] In clinical studies, virologic and immunologic response to nelfinavir-based therapy has varied according to the patient's age or prior history of ART, the number of drugs included in the combination regimen, and dose of nelfinavir used.

*Pharmacokinetics: Exposure-Response Relationships*

The relatively poor ability of nelfinavir to control plasma viremia in infants and children in clinical trials may be related to lower potency compared with other PIs or non-nucleoside reverse transcriptase inhibitors, as well as highly variable drug exposure, metabolism, and poor patient acceptance of available formulations.[10-12]

Administration of nelfinavir with food increases nelfinavir exposure (area under the curve increased by as much as five fold) and decreases pharmacokinetic (PK) variability relative to the fasted state. Drug exposure may be even more unpredictable in pediatric patients than in adults because of increased clearance of nelfinavir observed in children, and difficulties in taking nelfinavir with sufficient food to improve bioavailability. A slurry made by dissolving nelfinavir tablets in water or other liquids can be administered to children who are unable to swallow tablets. The bioavailability of dissolved nelfinavir tablets is comparable to that of tablets swallowed whole.[1,13]

Nelfinavir is metabolized by multiple CYP-450 enzymes including CYP3A4 and CYP2C19. M8, the major oxidative metabolite, has *in vitro* antiviral activity comparable to the parent drug. The variability of drug exposure at any given dose is much higher for children than for adults,[14] 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.[15,16] Analysis of data from PACTG 377 and PACTG 366 showed that CYP2C19 genotypes altered nelfinavir PKs and the virologic responses to combination therapy in children with HIV infection. These findings suggest that CYP2C19 genotypes are important determinants of nelfinavir PKs and virologic response in children with HIV infection.[10]

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.[17-19]

In a study of 32 children treated with nelfinavir 90 mg/kg/day divided into 2 or 3 doses a day, 80% of children with morning trough nelfinavir plasma concentration >0.8 mcg/mL had Week 48 HIV RNA concentrations <50 copies/mL, compared with only 29% of those with morning trough <0.8 mcg/mL.[20] It is of note that the median age of the group with $C_{trough}$ <0.8 mcg/mL was 3.8 years, while the median age of the group with $C_{trough}$ >0.8 mcg/mL was 8.3 years.[20]

Therapeutic drug monitoring (TDM) of nelfinavir plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with nelfinavir.[17,21] Similarly, better virologic responses were demonstrated in two pediatric trials in which TDM was used to guide dosing[16,22] and doses higher than those recommended in adults may be required in some patients. Infants have even lower drug exposures and higher variability in plasma concentrations than children who weigh <25 kg. The presence of lower peak drug concentrations and higher apparent oral clearance suggests that both poor absorption and more rapid metabolism may be contributing factors.[23,24] Given the higher variability of nelfinavir plasma concentrations in infants and children, nelfinavir is not recommended for use in children younger than age 2 years.

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# Saquinavir (SQV, Invirase) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Capsules:** 200 mg

**Tablets:** 500 mg

## Dosing Recommendations

### Neonate and Infant Dose:

- Not approved for use in neonates/infants.

### Pediatric Dose:

- Not approved for use in children and adolescents aged <16 years.

### Investigational Doses in Treatment-Experienced Children:

- Saquinavir must be boosted with ritonavir.

*Aged <2 Years:*

- No dose has been determined.

**Aged ≥2 Years (Conditional Dosing Based on Limited Data; See Text):**

| Weight (kg) | Dose Saquinavir plus Ritonavir |
|---|---|
| 5 to <15 kg | Saquinavir 50 mg/kg plus ritonavir 3 mg/kg, both twice daily |
| 15 to <40 kg | Saquinavir 50 mg/kg plus ritonavir 2.5 mg/kg, both twice daily |
| ≥40 kg | Saquinavir 50 mg/kg plus ritonavir 100 mg, both twice daily |

### Adolescent (Aged ≥16 years) and Adult Dose:

- Saquinavir should **only** be used in combination with ritonavir.
- Saquinavir 1000 mg plus ritonavir 100 mg, both twice daily.

## Selected Adverse Events

- Gastrointestinal intolerance, nausea, and diarrhea
- Headache
- Elevated transaminases
- Hyperlipidemia
- Hyperglycemia
- Fat maldistribution
- Increased bleeding episodes in patients with hemophilia
- PR interval prolongation, QT interval prolongation, and ventricular tachycardia (*Torsades de Pointes*) have been reported.

## 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 and saquinavir is contraindicated in patients with a prolonged QT interval.

## Metabolism/Elimination

- Cytochrome P (CYP) 450 3A4 and inhibitor, 90% metabolized in the liver.
- Use in patients with hepatic impairment: use with caution.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- Saquinavir is both a substrate and inhibitor of the 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 hemophiliacs, pancreatitis, and elevation in serum transaminases. The combination of saquinavir and ritonavir could lead to prolonged PR and/or QT 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 (see http://www.iasusa.org/sites/default/files/tam/22-3-642.pdf) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

Saquinavir is not Food and Drug Administration-approved for use in children or adolescents younger than 16 years of age.

*Efficacy*

Saquinavir has been studied with nucleoside reverse transcriptase inhibitors (NRTIs) and other protease inhibitors (PIs) in HIV-infected children.[1-6] Saquinavir/ritonavir and saquinavir/lopinavir/ritonavir regimens were considered for salvage therapy in children prior to the emergence of the new classes of antiretroviral medications. As dual PI therapy is no longer recommended in adult or pediatric guidelines, The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV does not recommend the use of saquinavir/lopinavir/ritonavir combination.[1,3-9]

*Pharmacokinetics*

Studies suggest that saquinavir should not be used without ritonavir boosting. A pharmacokinetic (PK) analysis of 5 children younger than 2 years and 13 children aged 2 to 5 years, using a dose of 50 mg/kg twice daily with ritonavir boosting, demonstrated that drug exposure was lower in children younger than 2 years whereas drug exposure was adequate in those aged 2 to 5 years.[10] For this reason, saquinavir should not be administered to children aged <2 years. In children aged ≥2 years, a dose of 50 mg/kg twice daily (maximum dose = 1000 mg) boosted with ritonavir 3 mg/kg twice daily (patients weighing 5 to <15 kg) or 2.5 mg/kg twice daily (patients weighing 15–40 kg) resulted in area under the curve and steady-state trough plasma concentration ($C_{trough}$) values similar to those in older children[7,8] and adults.

In a study of 50 Thai children, saquinavir/lopinavir/ritonavir was initiated as second-line therapy based on extensive NRTI resistance (saquinavir was dosed at 50 mg/m$^2$ body surface area and lopinavir/ritonavir was dosed at 230/57.5 mg/m$^2$ body surface area, all twice daily). After 96 weeks, 74% of the children achieved an undetectable plasma RNA load at <50 copies/mL. Therapeutic drug monitoring was used to establish adequate minimum plasma concentration ($C_{min}$) values and to aid with alterations in drug dosage based upon toxicity. Most $C_{min}$ values for saquinavir were above the desired trough value of 0.1 mg/L. The average $C_{min}$ throughout 96 weeks for saquinavir was 1.37 mg/L, and when saquinavir doses were adjusted, most were decreased by an average of 21% (8 mg/kg).[7,8]

*Toxicity*

In a healthy adult volunteer study, saquinavir/ritonavir use was associated with increases in both QT and PR intervals.[11,12] Rare cases of *Torsades de Pointes* and complete heart block have been reported in post-marketing surveillance. Saquinavir/ritonavir is not recommended for 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 AV block, or receiving other drugs that prolong QT interval. An electrocardiogram is recommended before initiation of therapy with saquinavir and should be considered during therapy.

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# Tipranavir (TPV, APTIVUS) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 used with ritonavir boosting. The ritonavir boosting dose used for tipranavir is higher than that used for other protease inhibitors.

### Pediatric Dose (Aged <2 Years):

- Not approved for use in children aged <2 years.

### Pediatric Dose (Aged 2–18 Years):

**Note:** Not recommended for treatment-naive patients

*Body Surface Area Dosing:*

- Tipranavir 375 mg/m$^2$ plus ritonavir 150 mg/m$^2$, both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

*Weight-Based Dosing:*

- Tipranavir 14 mg/kg plus ritonavir 6 mg/kg, both twice daily (maximum tipranavir 500 mg plus ritonavir 200 mg, both twice daily)

### Adult Dose:

**Note:** Not recommended for treatment-naive patients

- Tipranavir 500 mg (two 250-mg capsules) plus ritonavir 200 mg, both twice daily

## 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 with food.
- Tipranavir oral solution contains 116 IU vitamin E/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 bottle is 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;
- Dosing in patients with renal impairment: No dose adjustment required
- Dosing in patients with hepatic impairment: No dose adjustment required for mild hepatic impairment; use contraindicated for moderate-to-severe hepatic impairment.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- Tipranavir has the potential for multiple drug interactions. Co-administration of tipranavir/ritonavir (TPV/r) with drugs that are highly dependent on CYP3A 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 coadministered.
- 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 (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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

### *Pediatric Use*

*Approval and General Considerations*

Tipranavir is approved for use in children as young as 2 years and is available in a liquid formulation. Its indication is limited to those patients who are treatment-experienced and infected with HIV strains resistant to more than one protease inhibitor (PI).[1] The use of tipranavir is limited by the high pill burden imposed on patients taking tipranavir capsules, including the need for a higher dose of boosting ritonavir than is required with other PIs. This increased dose of ritonavir is associated with 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*

Food and Drug Administration approval of tipranavir was based on a multicenter, pediatric study of the safety, efficacy, and pharmacokinetics (PKs) of TPV/r in children with HIV infection (PACTG 1051/BI-1182.14).[2] This study enrolled 110 treatment-experienced children (with the exception of 3 treatment-naive patients) aged 2 to 18 years (median age 11.7 years). Patients were randomized to receive two different dosing regimens. The higher dose of TPV/r (375 mg/150 mg/m$^2$ body surface area 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. The 5-year, long-term follow-up study to evaluate safety, efficacy, and tolerability of patients enrolled in PACTG 1051 was reported.[3] At week 288, most children were no longer receiving TPV/r. Reasons for discontinuation included AEs, virologic failure, and non-adherence. The youngest patients who were stable at week 48 were more likely to still be on treatment after 5 years with continued efficacy.[3]

### *Pharmacokinetics*

PK evaluation of the liquid formulation at steady state in children was assessed.[4] In children aged 2 to <12 years, at a dosage of TPV/r 290/115 mg/m$^2$ body surface area, tipranavir trough concentrations 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 (375/150 mg/m$^2$ body surface area, 30% higher than the directly scaled adult dose) to achieve drug exposure similar to that in adults receiving the standard TPV/r dose. Based on these studies, the final dose of TPV/r 375/150 mg/m$^2$ body surface area twice daily is recommended.

### *Toxicity*

AEs were similar between treatment groups in the multicenter, pediatric study.[2] Twenty-five percent of children experienced a drug-related serious AE, and 9% of patients discontinued study drugs because of AEs. The most common AEs were gastrointestinal disturbances: 37% of participants had vomiting and 24% had diarrhea. The most common Grade 3 through 4 laboratory abnormalities were increases in CPK (11%), alanine aminotransferase (6.5%), and amylase (7.5%). In the long-term follow-up report for PACTG 1051, incidence of AEs defined as drug-related was 55% to 65% regardless of age at entry, with higher discontinuation rates due to AEs in the older age groups.[3]

Vitamin E is an excipient in the tipranavir oral solution, with a concentration of 116 IU of vitamin E and 100 mg tipranavir/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 (10 IU) and close to the upper limit of tolerability for children. In PACTG 1051, bleeding events were reported more commonly in children receiving tipranavir oral capsules (14.3%) than in children taking tipranavir oral solution (5.75%).[2] Overall, the incidence of bleeding episodes (primarily epistaxis) in pediatric patients observed in clinical trials was 7.5%.[5]

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## Entry and Fusion Inhibitors

Enfuvirtide (T-20, Fuzeon)

Maraviroc (MVC, Selzentry)

# Enfuvirtide (T-20, Fuzeon) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents] and http://www.hiv-druginteractions.org/)

- There are no known significant drug interactions with enfuvirtide.

***Major Toxicities***

- *More common:* Almost all patients (87% to 98%) experience local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are usually mild to moderate in severity but can be more severe. Average duration of local injection site reaction is 3 to 7 days, but was >7 days in 24% of patients.
- *Less common (more severe):* Increased rate of bacterial pneumonia (unclear association).[1] Pediatric studies have lacked the statistical power to answer questions concerning enfuvirtide use and increased risk of pneumonia.
- *Rare:* Hypersensitivity reactions (HSRs) (<1%) including fever, nausea and vomiting, chills, rigors, hypotension, and elevated liver transaminases; immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients experiencing HSRs should seek immediate medical attention. Therapy should not be restarted in patients with signs and symptoms consistent with HSRs.
- *Pediatric specific:* Local site cellulitis requiring antimicrobial therapy (up to 11% in certain subgroups of patients in pediatric studies).[2]

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

Resistance testing must be ordered specifically for fusion inhibitors, as it is not performed on routine genotypic or phenotypic assays.

***Pediatric Use***

*Approval*

Although enfuvirtide is Food and Drug Administration (FDA)-approved for use in children, it is not commonly used because of its high cost, need for twice-daily subcutaneous (SQ) injections, and high rate of injection site reactions. Use in deep salvage regimens[3] has also declined with the availability of integrase inhibitors and other entry inhibitors (such as maraviroc).

*Pharmacokinetics*

A single-dose pharmacokinetic evaluation study of enfuvirtide, given SQ to 14 children with HIV infection aged 4 to 12 years (PACTG 1005), identified that enfuvirtide 60 mg/m$^2$ of body surface area per dose resulted in a target trough concentration that approximated the equivalent of a 90-mg dose delivered SQ to an adult (1000 mg/mL).[4] In a second pediatric study of 25 children aged 5 to 16 years, a 2-mg/kg dose (maximum 90 mg) of enfuvirtide given twice daily yielded drug concentrations similar to 60 mg/m$^2$ of body surface area dose independent of age group, body weight, body surface area, and sexual maturation.[5] The FDA-recommended dose of enfuvirtide for children aged 6 to 16 years is 2 mg/kg (maximum 90 mg) administered SQ twice daily. Further data are needed for dosing in children aged <6 years.

*Efficacy*

The safety and antiretroviral (ARV) activity of twice-daily SQ enfuvirtide administration at 60 mg/m$^2$ per dose plus optimized background therapy (OBT) was evaluated over 96 weeks in 14 children aged 4 to 12 years who had failed to achieve viral suppression on multiple prior ARV regimens (PACTG 1005). At 24 weeks 71% of the children had a $>1.0_{log}$ reduction in viral load; 43% and 21% had HIV RNA levels suppressed to <400 copies/mL and <50 copies/mL, respectively. However, only 36% of children maintained virologic suppression ($>1.0_{log}$ decrease in HIV RNA) at Week 96. Most children had local injection site reactions.[6] Significant improvements in CD4 T lymphocyte (CD4) cell percentages and height *z* scores were observed in children receiving enfuvirtide for 48 and 96 weeks.

T20-310, a Phase I/II study of enfuvirtide (2.0 mg/kg SQ, maximum 90 mg, twice daily) plus OBT, enrolled 52 treatment-experienced children aged 3 to 16 years for 48 weeks. Only 64% of the children completed 48 weeks of therapy. The median decrease in HIV RNA was -1.17 $\log_{10}$ copies/mL (n = 32) and increase in CD4 cell count was 106 cells/mm$^3$ (n = 25). At Week 8, treatment responses as measured by several plasma HIV RNA parameters were superior in younger children (aged <11 years) compared with adolescents. Median increases in CD4 cell count were 257 cells/mm$^3$ in children and 84 cells/mm$^3$ in adolescents. Local skin reactions were common in all age groups (87% of study participants). The observed differential responses between children and adolescents probably reflect unique challenges to adherence with the prescribed regimen.[2]

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# Maraviroc (MVC, Selzentry) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Tablets:** 25 mg, 75mg, 150 mg and 300 mg

**Oral Solution:** 20 mg/mL

## Dosing Recommendations

### Neonate/Infant Dose:

- Not approved for use in neonates/infants.

### Pediatric Dose:

- Approved for use by children aged ≥2 years and weighing ≥10 kg

**Recommended Dosage in Antiretroviral Experienced Children Aged ≥2 Years and Weighing ≥10 kg: Tablets or Oral Suspension**

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]):

| Weight Band | Twice-Daily Dosing | Liquid 20 mg/mL | Tablets |
|---|---|---|---|
| 10 kg to <20 kg | 50 mg | 2.5 mL | 2 25-mg |
| 20 kg to <30 kg | 75 mg | 4 mL | 1 75-mg |
| 30 kg to <40 kg | 100 mg | 5 mL | 1 25-mg & 1 75-mg |
| >40 kg | 150 mg | 7.5 mL | 1 150-mg |

When given with nucleoside reverse transcriptase inhibitors (NRTIs), enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers:

| Weight Band | Twice-Daily Dosing | Liquid 20 mg/mL | Tablets |
|---|---|---|---|
| 10 kg to <20 kg | Not recommended | | |
| 20 kg to <30 kg | Not recommended | | |
| 30 kg to <40 kg | 300 mg | 15 mL | 1 300-mg |
| >40 kg | 300 mg | 15 mL | 1 300-mg |

When given with potent CYP3A inducers including efavirenz and etravirine (without a potent CYP3A inhibitor):

Not recommended

## Selected Adverse Events

- Vomiting, diarrhea
- Cough
- Upper respiratory tract infections
- Dizziness
- Fever
- Rash
- Hepatotoxicity (which may be preceded by severe rash and/or other signs of systemic allergic reaction)
- Postural hypotension (generally in patients with severe renal insufficiency)

## Special Instructions

- Maraviroc is recommended for patients with only CCR5-tropic HIV-1. Conduct testing with HIV tropism assay (see Antiretroviral Drug-Resistance Testing in Adult and Adolescent Antiretroviral Guidelines) before using MVC to exclude the presence of CXCR4-using or mixed/dual-tropic HIV. Do not use if CXCR4 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
- Dosing of maraviroc in patients with hepatic impairment: Use caution when administering maraviroc to patients with hepatic impairment. Because maraviroc is metabolized by the liver, concentrations may be increased in patients with hepatic impairment.
- Dosing of maraviroc in adults and adolescents with renal impairment: refer to the

**Adult Dose**

| | |
|---|---|
| When given with potent CYP3A inhibitors (with or without a potent CYP3A inducer) including PIs (except TPV/r) and EVG/r | 150 mg twice daily |
| When given with NRTIs, enfuvirtide, TPV/r, nevirapine, raltegravir, and other drugs that are not potent CYP3A inhibitors or inducers | 300 mg twice daily |
| When given with potent CYP3A inducers including efavirenz and etravirine (without a potent CYP3A inhibitor) | 600 mg twice daily |

manufacturer's prescribing information.

- Data are insufficient to make dosing recommendations for use of maraviroc in children concomitantly receiving non-interacting medications and weighing less than 30 kg or in all children concomitantly receiving potent CYP3A inducers without a potent CYP3A inhibitor.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

***Absorption***

Absorption of maraviroc is slightly reduced with ingestion of a high-fat meal. There were no food restrictions in the adult trials (using the tablet formulation) or in the pediatric trial (using 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 (Pgp) substrate and requires dosage adjustments when administered with CYP- or Pgp-modulating medications.

Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with maraviroc; recommended maraviroc dosages 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, and dizziness.
- *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 fewer than 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. The International AIDS Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10). Clinical failure may also represent the outgrowth of CXCR4-using (naturally resistant) HIV variants.

***Pediatric Use***

*Approval*

Maraviroc is approved by the Food and Drug Administration in children aged ≥2 years and weighing ≥10 kg who have CCR5-tropic HIV-1.[1]

*Pharmacokinetics and Efficacy*

The pharmacokinetics, safety, and efficacy of maraviroc have been examined in a dose-finding and efficacy study involving treatment experienced children aged 2 to 17 years weighing at least 10 kg and having HIV-1 plasma RNA >1000 copies/mL. In this trial, maraviroc dose was based upon body surface area and the composition of the optimized background therapy: most (90/103; 87%) received maraviroc in combination with potent CYP3A inhibitors, and only 3 participants received maraviroc with CYP3A inducers. The key pharmacologic target (geometric mean $C_{average}$ of >100 ng/mL) was achieved with both the tablet and oral solution formulations of maraviroc. From a mean baseline plasma HIV-1 RNA of 4.4 $\log_{10}$ copies/mL, a decrease of ≥1 $\log_{10}$ occurred in all 4 age-based cohorts. Overall, 48% of participants achieved a decrease to <48 copies/mL at Study Week 48 and 65% of subjects achieved plasma HIV-1 RNA <400 copies/mL. The most common maraviroc-related AEs through 48 weeks were diarrhea (16.5%), vomiting (16.5%), and upper respiratory infections (13.6%).[2]

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## Integrase Inhibitors

Dolutegravir (DTG, Tivicay, GSK1349572)

Elvitegravir (EVG)

Raltegravir (RAL, Isentress)

# Dolutegravir (DTG, Tivicay) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Tablet:** 10 mg, 25 mg, and 50 mg

**Fixed-Dose Combination Tablet:**

- [*Triumeq*] Abacavir 600 mg plus dolutegravir 50 mg plus lamivudine 300 mg

## Dosing Recommendations

### Neonate/Infant Dose:

- Not approved for use in neonates/infants

### Children Weighing ≥30 to <40 kg:

- Not Food and Drug Administration-approved for use in children weighing <30 kg.
- A clinical trial in antiretroviral (ARV) treatment-experienced (but integrase strand inhibitor [INSTI]-naive children) weighing <30 kg is underway (see text).

| Body weight (kg) | Dose[a] (mg/day) | Dosing Frequency | Tablet Size (mg) |
|---|---|---|---|
| 30 to <40 | 35 | Once daily | One 10-mg tablet plus one 25-mg tablet |

[a] These doses are for children who are ARV-naive or ARV-experienced (but INSTI-naive) and who are not being treated with UGT1A1/CYP3A inducers

**Note:** Dolutegravir 10-mg and 25-mg tablets may be available in the retail pharmacy. If not available, when ordering dolutegravir 10-mg or 25-mg tablets, have the pharmacy contact their drug wholesaler and tell the drug wholesaler to order directly from the GSK distribution center. The GSK distribution center will ship the formulation directly to the pharmacy.

## Selected Adverse Events

- Insomnia
- Headache
- 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**.[1]
- The efficacy of 50-mg dolutegravir twice daily is reduced in patients with certain combinations of INSTI-resistance mutations (see Resistance section below).

## Metabolism/Elimination

- UGT1A1 and cytochrome P450 (CYP) 3A substrate
- 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

**Children and Adolescents (Weighing ≥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[a] | 50 mg twice daily |

[a] Combinations that do not include metabolic inducers should be considered where possible.

### Combination Tablet

*[Triumeq] Abacavir plus Dolutegravir plus Lamivudine:*

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

- 1 tablet once daily
- For use in patients who are ARV treatment-naive or treatment-experienced (but INSTI-naive) and not being treated with UGT1A1/CYP3A inducers

serum creatinine, but does not affect glomerular filtration.

- 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Dolutegravir is a UGT1A1 and cytochrome 3 (CYP3) A substrate and may require dosage 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 counteracts this effect on dolutegravir concentrations. Dolutegravir should not be administered with nevirapine because of insufficient data.
- 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.

***Resistance***

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10), and the Stanford University HIV Drug Resistance database offers a discussion of integrase strand transfer inhibitor (INSTI) mutations (http://hivdb.stanford.edu/DR/). The efficacy of 50-mg dolutegravir twice daily is reduced in patients with INSTI-resistance Q148 substitution plus 2 or more additional INSTI-resistance mutations: T66A, L74I/M, E138A/K/T, G140SA/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

### *Pediatric Use*

*Approval*

Dolutegravir is Food and Drug Administration (FDA)-approved in combination with other antiretroviral drugs for children weighing at least 30 kg and who are treatment-naive or treatment-experienced but integrase strand transfer inhibitor (INSTI)-naive.[2]

### *Efficacy and Pharmacokinetics*

IMPAACT P1093 is an ongoing open-label trial of children with HIV with the plan to enroll down to age 4 weeks. FDA approval of dolutegravir down to age 12 years/40 kg was based on data from 23 treatment-experienced, INSTI-naive adolescents.[3] Intensive pharmacokinetic (PK) evaluations were performed on the first 10 participants (9 weighing ≥40 kg and receiving 50 mg, 1 weighing 37 kg and receiving 35 mg) and 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 to 10 days after dolutegravir was started). An additional 13 participants were then enrolled for evaluation of long-term outcomes. At 48 weeks, 61% had achieved HIV RNA concentration <50 copies/mL. No safety or tolerability concerns were identified. By week 144, 39% and 30% had achieved HIV RNA concentrations <400 and <50 copies/mL, respectively. All who experienced virologic failure were nonadherent. In addition, a younger cohort of children aged ≥6 to <12 years are undergoing PK and longer-term follow-up in P1093, with those weighing ≥30 to <40 kg receiving the 35-mg dose and those weighing ≥40 kg using the 50-mg dose. At 48 weeks, data from 23 participants have demonstrated a favorable safety profile, adequate PK, and virologic efficacy with HIV RNA concentration of <50 copies/mL achieved in 74% (17/23).[3,4] This has led to FDA approval of the lower-strength tablets for children with HIV as young as 6 years and with body weight as low as 30 kg. The European Medicines Agency has approved the lower-strength tablets for children aged ≥6 years weighing ≥15 kg based on population PK modelling and simulation analyses.[5] These analyses support a dose of 20 mg for children weighing 15 to <20 kg and 25 mg for those weighing 20 to <30 kg. An oral pediatric granule formulation and a dispersible tablet are also being studied, though the granule formulation will be replaced by the dispersible tablet. Doses for younger children are also under investigation in P1093.

**Pharmacokinetics of Dolutegravir in Adult and Pediatric Studies**

| Population of Study | Weight (kg) | Dose (mg/day) | Tablet Size (mg) | Dosing Frequency | Dose for Lowest Weight in Weight Band (mg/kg) | Trough Plasma Concentrationa mcg/mL[b] |
|---|---|---|---|---|---|---|
| **Adults with Prior INSTI Treatment** | >40 | 100 | 50 | Twice daily | 2.5 | 2.12 (47) |
| **Adults without Prior INSTI Treatment** | ≥40 | 50 | 50 | Once daily | 1.25 | 1.11 (46) |
| **Children without Prior INSTI Treatment (N = 14)** | ≥40 | 50 | 50 | Once daily | 1.25 | 0.99 (66) |
| **Children without Prior INSTI Treatment (N = 3)** | 30 to <40 | 35 | 10 plus 25 | Once daily | 1.17 | 1.33 (93) |

[a] Source: Dolutegravir [package insert]. Food and Drug Administration. 2016. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204790Orig1s008lbl.pdf

[b] Geometric mean (percent coefficient of variation)

**Note:** Recommendations for 100 mg/day are for adults in special circumstances using 50 mg twice daily (see product label or text above).

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 semisolid food or liquid, all of which should be consumed **immediately**.[1] 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.[6]

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# Elvitegravir (EVG, VITEKTA) (Last updated April 27, 2017; last reviewed April 27, 2017)

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:**

- [*Stribild*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir disoproxil (TDF) 300 mg
- [*Genvoya*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide (TAF) 10 mg

## Dosing Recommendations

**Note:** Elvitegravir is only available in fixed-dose combination tablets with the pharmacokinetic (PK) enhancer (boosting agent) cobicistat (i.e., Stribild or Genvoya).

### Pediatric Dose (Weighing <35 kg):

- No data on appropriate dose of elvitegravir in Stribild in children weighing <35 kg.
- Studies ongoing for dosing of Genvoya in children aged 6 to <12 years weighing 25 to <35 kg.

### Adolescent (Weighing >35 kg) and Adult Dose:

*Genvoya (Any Sexual Maturity Rating; Tanner Stage):*[a]

- One tablet once daily

*Stribild (SMR 4 or 5)*[a]*:*

- One tablet once daily

## Selected Adverse Events

- Diarrhea (elvitegravir)
- Stribild-associated adverse events: Nausea, diarrhea, fatigue, headache. TDF—renal insufficiency, decreased bone mineral density, flatulence; cobicistat—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 used in combination with 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 increase in serum creatinine >0.4 mg/dL should be closely monitored for renal safety.
- Screen patients for hepatitis B virus (HBV) infection before use of emtricitabine, TDF, or TAF. Severe acute exacerbation of HBV can occur when emtricitabine, TDF, or TAF is 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 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 PK enhancer (boosting agent) cobicistat in Stribild or Genvoya. Refer to TDF and TAF sections 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.

[a] Stribild and Genvoya are Food and Drug Administration-approved for use in antiretroviral (ARV) treatment-naive adults or to replace the current ARV regimen in adults who are 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 Stribild or Genvoya.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Stribild and Genvoya contain elvitegravir and cobicistat. 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-glycoprotein and the organic anion-transporting polypeptides OAT1B1 and OAT1B3. Potential exists 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.
- *Protease inhibitors:* Neither Stribild nor Genvoya should be administered concurrent with products or regimens containing ritonavir because of similar effects of cobicistat and ritonavir on CYP3A metabolism. Cobicistat and ritonavir are not interchangeable, and when administered with either atazanavir or darunavir, may result in different drug interactions when used with other concomitant medications.
- 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 (NRTIs) 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, including increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate, has been observed with TDF. 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/). There is phenotypic cross-resistance between elvitegravir and raltegravir.[1]

***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 (PI) plus ritonavir and was FDA-approved in 2012 for use in adults as the fixed-dose combination product Stribild, which contains elvitegravir, cobicistat, emtricitabine, and TDF. Neither Vitekta nor Stribild is FDA-approved for use in children aged <18 years.[2,3] In November 2015, Genvoya, which contains elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (TAF) was FDA-approved for use in youth aged ≥12 years and weighing ≥35 kg.[4]

Gilead removed Vitekta from the market in February 2017.

*Efficacy in Clinical Trials*

At 144 weeks in adults, a combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be non-inferior to a regimen of efavirenz/emtricitabine/TDF[5] and to a regimen of atazanavir/ritonavir (ATV/r) with emtricitabine/TDF.[6] In 2 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; $P < 0.0001$).[7]

*Formulations*

Elvitegravir is an integrase strand transfer inhibitor that is metabolized rapidly by CYP3A4. Elvitegravir must be used in combination with a PI co-administered with ritonavir and another ARV drug, in the fixed-dose combination product Stribild,[3] or Genvoya,[4] 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.[8] Both ritonavir and cobicistat slow elvitegravir metabolism and allow once-daily administration of elvitegravir when used in approved doses and combinations. Note that the dose of elvitegravir is different when used with ATV/r or lopinavir compared to its use with different PIs plus ritonavir, or compared to its use with cobicistat as a component of Stribild or Genvoya. Complex or unknown mechanisms of drug interactions between cobicistat or ritonavir with elvitegravir and PIs may result in different drug interactions when used with other medications.[8]

Stribild is FDA-approved as a complete antiretroviral therapy (ART) regimen in antiretroviral (ARV)-naive adults with HIV-1 aged ≥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.[3] Trials have shown non-inferiority of Stribild to regimens of emtricitabine combined with TDF plus ATV/r,[9,10] or emtricitabine plus TDF plus efavirenz.[11,12] 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.[13] Adults who experience a confirmed increase in serum creatinine greater than 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.[3] Careful periodic evaluation of renal function is warranted, because TDF is included in Stribild and can be associated with renal toxicity. This nephrotoxicity may be more pronounced in patients with pre-existing renal disease.[3]

Genvoya is FDA-approved as a complete ART regimen in ARV-naive individuals with HIV-1 aged ≥12 years and weighing ≥35 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.[3] Because Genvoya contains TAF instead of TDF, Genvoya would be expected to have less bone and renal toxicity compared to Stribild. Diminished renal and bone toxicity of Genvoya has been shown in two studies in adults in which, compared to those treated with Stribild, participants treated with Genvoya had significantly smaller increase in serum creatinine, less proteinuria, and smaller decreases in BMD at the spine and hip after 48 weeks of treatment.[7]

*Use of Elvitegravir as Vitekta in Adolescents Aged 12 to 18 Years*

A PK study of the adult dose of elvitegravir as Vitekta in 25 youth aged 12 to 18 years showed plasma concentrations similar to those in adults when given in regimens that included ATV/r or lopinavir/ritonavir (LPV/r) in addition to NRTIs. However, the elvitegravir trough plasma concentration was lower when co-administered with darunavir/ritonavir, tipranavir/ritonavir, or fosamprenavir/ritonavir than when it was co-administered with ATV/r or LPV/r, even though the lower elvitegravir dose was used when given with atazanavir/ritonavir or LPV/r.[14] This was a multi-pill regimen and medication adherence was poor during the 48-week treatment phase of the study. Data were insufficient to establish safety and effectiveness of elvitegravir as Vitekta in this age group. Therefore, elvitegravir as Vitekta was not FDA-approved for use in this age group.[2]

*Use of Elvitegravir as Stribild or Genvoya in Adolescents Aged 12 to 18 years*

Studies of the adult dosage formulation of Stribild in youth with HIV aged ≥12 years and weighing ≥35 kg have demonstrated PK, safety, and efficacy similar to that in adults through 24 weeks of study.[15-18] Studies of the adult dosage formulation of Genvoya in youth with HIV aged ≥12 years and weighing ≥35 kg have shown safety comparable to that of adults,[19] and this formulation is FDA-approved for use in this age/weight group. Because of the diminished renal and bone toxicity of Genvoya compared to Stribild, Genvoya might be preferable to Stribild for treatment of youth with sexual maturity rating 1 to 3. In 24 pediatric subjects aged 12 to <18 years who received Genvoya, the TAF area under the curve was decreased 23% compared to exposures achieved in treatment-naive adults.[4] The clinical significance of this is unclear.

*Use of Elvitegravir as Vitekta in Children Aged Younger Than 12 years*

In children aged ≥6 years and weighing ≥30 kg, when elvitegravir 85 mg (the adult dose) was co-administered in regimens containing either LPV/r or ATV/r, elvitegravir exposures were similar to those in adults.[20] Pediatric formulations of both elvitegravir[21] and cobicistat[22] are bioequivalent to adult formulations.

*Use of Elvitegravir as Genvoya in Children Aged 6 to <12 years*

Studies are ongoing of Genvoya in children aged 6 to <12 years and weighing ≥25 kg.[23]

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# Raltegravir (RAL, Isentress) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

## Formulations

**Tablets:** 400 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 5 mL of water for final concentration of 20 mg/mL.

**Note:** Film-coated tablets, chewable tablets, and oral suspension **are not interchangeable**.

## Dosing Recommendations

### Neonate Dose:

- Not approved for use in neonates.
- Investigational dose for neonates ≥37 weeks of gestation and weighing ≥2 kg under study in IMPAACT P1110:
  - Birth to age 7 days: 1.5 mg/kg once daily
  - Aged 8–28 days: 3 mg/kg twice daily
  - Aged ≥4 weeks: 6 mg/kg twice daily (see below for approved infant and pediatric dose)
  - No dosing information is available for preterm or low birthweight infants.

**Note:** Metabolism by uridine diphosphate glucotransferase (UGT1A1) is low at birth and increases rapidly over the next 4–6 weeks of life.

### Infant and Pediatric Dose:

**Oral Suspension Dosing Table**[a]

*Children Aged ≥4 Weeks and Weighing ≥3 kg to <20 kg:*

| Body Weight (kg) | Volume (Dose) of Suspension to be Administered |
|---|---|
| 3 to <4 | 1 mL (20 mg) twice daily |
| 4 to <6 | 1.5 mL (30 mg) twice daily |
| 6 to <8 | 2 mL (40 mg) twice daily |
| 8 to <11 | 3 mL (60 mg) twice daily |
| 11 to <14 | 4 mL (80 mg) twice daily |
| 14 to <20 | 5 mL (100 mg) twice daily |

[a] 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 5 mL (100 mg) twice daily.

## 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.
- Avoid taking aluminum and/or magnesium containing antacids.
- Chewable tablets can be chewed, crushed (before administration), or 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 original package with desiccant to protect from moisture.
- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- Oral suspension is provided with a kit that includes two mixing cups, two dosing syringes, and 60 foil packets. Detailed

**Note:** For children weighing 11–20 kg, either oral suspension or chewable tablets can be used.

**Pediatric Dose for Chewable Tablets and Film-Coated Tablets:**

*Children Weighing ≥11 kg:*

- <25 kg: Chewable tablet twice daily. See table below for chewable tablet dose.
- ≥25 kg: 400-mg film-coated tablet twice daily **or** chewable tablets twice daily. See table below for chewable tablet dose.

**Chewable Tablet Dosing Table[a]**

**Note:** Maximum dose of chewable tablets is 300 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[b] twice daily |
| 28 to <40 | 200 mg twice daily | 2 X 100 mg twice daily |
| ≥40 | 300 mg twice daily | 3 X 100 mg twice daily |

[a] The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

[b] The 100-mg chewable tablet can be divided into equal halves.

**Film-Coated Tablets**

*Child/Adolescent Weighing ≥25 kg and Adult Dose:*

- 400-mg film-coated tablet twice daily

instructions are provided in the Instructions for Use document. Each foil, single-use packet contains 100 mg of raltegravir, which will be suspended in 5 mL of water for final concentration of 20 mg/mL. 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
- Dosing of raltegravir in patients with hepatic impairment: No dosage adjustment is necessary for patients with mild-to-moderate hepatic insufficiency. No dosing information is available for patients with severe hepatic impairment.
- Dosing of raltegravir in patients with renal impairment: No dosage adjustment necessary.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *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, whereas inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir (no dosing modifications are recommended when raltegravir is co-administered with tipranavir/ritonavir or atazanavir/ritonavir).
- In adults, an increased dose of raltegravir is recommended when co-administered with rifampin. In adults receiving rifampin, the recommended raltegravir dose is 800 mg twice daily. The appropriate dose adjustment is not known in children and is currently being studied in IMPAACT P1101.
- Efavirenz and etravirine may decrease raltegravir concentrations (no dosing modifications are recommended when raltegravir is co-administered with efavirenz or etravirine).

- Before administration, a patient's medication profile should be carefully reviewed for potential drug interactions with raltegravir.
- Raltegravir plasma concentrations may be reduced when administered with antacids containing divalent metal cations such as magnesium hydroxide, aluminum hydroxide, or calcium carbonate:
  - Co-administration or administration of raltegravir within 6 hours of aluminum and/or magnesium hydroxide-containing antacids resulted in significantly reduced raltegravir plasma levels and is not recommended.
  - Calcium carbonate decreased raltegravir plasma concentrations to a lesser extent, thus no dose adjustment is recommended with calcium-containing antacids.

***Major Toxicities***

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, itching, and insomnia.
- *Less common:* Abdominal pain, vomiting. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening 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. Myopathy and rhabdomyolysis: Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, and paranoia especially in those with prior history. Rash including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis have been reported. 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 (see http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/DR/).

***Pediatric Use***

*Approval*

Raltegravir is an integrase strand transfer inhibitor indicated in combination with other antiretroviral (ARV) drugs for the treatment of HIV-1 infection for use in infants and children aged ≥4 weeks and weighing ≥3 kg. Current pediatric Food and Drug Administration approval and dosing recommendations are based upon evaluations in 122 patients aged ≥4 weeks to 18 years enrolled in IMPAACT P1066.[1]

Overall, raltegravir has a favorable safety profile and is available in formulations suitable for administration to infants and young children.

*Efficacy in Clinical Trials (Adults and Children):*

- Raltegravir has been evaluated in three large randomized clinical trials in adults, 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. However, with longer follow-up of 4 and 5 years, more patients discontinued efavirenz and raltegravir was found to be superior.[2-4] SPRING-2 compared raltegravir to dolutegravir and demonstrated non-inferiority of dolutegravir.[5] ACTG A5257 compared raltegravir to ATV/r and DRV/r; all regimens had equivalent virologic efficacy but raltegravir had better tolerability.[6]
- Raltegravir has been studied in infants, children and adolescents in an open-label trial, IMPAACT P1066, to evaluate pharmacokinetic (PK), safety, tolerability, and efficacy. In 96 children and adolescents aged 2 through 18 years, who were mostly treatment-experienced, 79.1% of the patients achieved a favorable viral load response (HIV viral load <400 copies/mL or ≥1 log10 decline in viral load) while receiving the currently recommended dose of raltegravir. Infants and toddlers aged ≥4 weeks to <2 years were also

enrolled in P1066 and received treatment with raltegravir oral suspension. At Weeks 24 and 48, 61% of the infants (14 of 23 infants) had an HIV viral load <400 copies/mL.[7-9]

### *Efficacy and Pharmacokinetics of Once-Daily Dosing (Adults)*

Raltegravir PK exhibit considerable intrasubject and intersubject variability.[10,11] Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naive patients with HIV were randomized to receive raltegravir 800 mg once daily 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 $C_{trough}$ concentrations below 45 nM were at the greatest risk of treatment failure.[10,11] Overall drug exposures were similar in both groups but the association between higher risk of treatment failure and lower $C_{trough}$ concentrations suggests that maintaining raltegravir trough plasma concentrations above 45 nM is important for efficacy.[10,11]

Higher once-daily doses of raltegravir may be as effective as 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either 1200 mg of once daily (two, 600 mg tablets) versus 400 mg twice daily plus tenofovir disoproxil fumarate plus emtricitabine. After 48 weeks, 88.9% on the once-daily dose versus 88.1% twice-daily reached viral loads <40 copies. There was no difference in discontinuation rates due to side effects.[12]

### *Efficacy and Pharmacokinetics (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.[8,9]

**Table A: Summary of P1066 Cohorts and Participation[8,9]**

| 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 P1066 PK Results by Cohort[8,9]**

| Age (years) | Cohort | Formulation | Intensive PK | Mean Dose mg/kg | GM (CV%)[a] $AUC_{0-12h}$ µMxh | GM (CV%)[b] $C_{12h}$ 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) |

[a] PK targets for Cohorts I-III: $AUC_{0-12h}$ 14-25 µMxh; $C_{12h}$ nM ≥33 nM

[b] PK targets for Cohorts IV-V: $AUC_{0-12h}$ 14-45 µMxh; $C_{12h}$ nM ≥75 nM

**Key to Acronyms:** AUC = area under the surve; GM = geometric mean; PK = pharmacokinetic

### *Children Aged 2 to 18 Years*

IMPAACT P1066 is a Phase I/II open-label multicenter study to evaluate the PK profile, safety, tolerability, and efficacy of various formulations of raltegravir in antiretroviral treatment (ART)-experienced children and adolescents with HIV aged 2 to 18 years in combination with an optimized background ART regimen.[9,13] Subjects received either the 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing at least 25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 to <12 years). In IMPAACT P1066, the initial dose-finding stage included intensive PK evaluation in various age cohorts (Cohort I: aged 12 to <19 years; Cohort II: 6 to <12 years, Cohort III: 2 to <6 years). Dose selection was based on achieving target PK parameters similar to those seen in adults: PK targets were geometric mean (GM) area under the curve ($AUC_{0\text{-}12h}$) of 14–25 µMxh 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 subjects 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 subjects completed 48 weeks of treatment with 79% achieving HIV RNA <400 copies/mL and 57% achieving HIV RNA <50 copies/mL, with a mean CD4 T lymphocyte (CD4) cell count (percent [%]) increase of 156 cells/µL (4.6%).[9] 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 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.[9] Overall, raltegravir administered as a film-coated tablet twice daily in subjects aged 6 to <19 years and 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.[14]

In 19 children and adolescents with HIV and multidrug-resistant virus in the HIV Spanish Pediatric Cohort (CoRISe), good virologic response and improved CD4 counts were observed when raltegravir was included in an optimized regimen.[7] Additional experience from the French expanded access program in treatment-experienced adolescents supports the good virologic and immunologic results observed in IMPAACT P1066.[15,16]

#### *Infants/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 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 infection, and 69% had baseline plasma HIV-1 RNA exceeding 100,000 copies/mL. PK targets for Cohorts IV and V were modified to GM $AUC_{0\text{-}12h}$ of 14 to 45 µMxh and GM 12-hour concentration ($C_{12h}$) ≥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, 2 subjects experienced AEs thought to be related to study drug: 1 patient with a serious erythematous rash that resulted in permanent discontinuation of raltegravir, and 1 patient with immune reconstitution inflammatory syndrome. Virologic success defined as ≥1 $\log_{10}$ decline in HIV RNA or <400 copies/mL at 48 weeks was achieved in 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 [%]) increase of 527.6 cells/mm$^3$ (7.3%) There were 4 subjects in Cohort IV with virologic failure by week 48 and 1 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.[8]

*Neonates Aged <4 Weeks*

There are limited data on the safety and dosing of raltegravir in 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 it is likely that raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for UGT and albumin binding sites.[17] Washout PK of raltegravir in neonates born to pregnant women with HIV was studied in IMPAACT P1097.[18] 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 I, multicenter trial enrolling full-term neonates exposed to HIV at high risk of acquiring HIV-1-infection, with or without *in utero* raltegravir exposure. Study design included 2 cohorts; Cohort 1 infants received 2 single raltegravir doses 1 week apart and Cohort 2 infants received daily raltegravir dosing for 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 this daily raltegravir dosing regimen for evaluation in raltegravir-naive 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.[19,20] Protocol exposure targets for each subject are $AUC_{24}$ 12-40mg*h/L, $AUC_{12}$ 6-20 mg*h/L, $C_{12}$ or $C_{24}$ > 33 ng/mL. Safety was assessed based on clinical and laboratory evaluations.[18,21,22] Twenty-six raltegravir-naive infants were enrolled in Cohort 2. Evaluable PK results and safety data are available for 25 infants. Results for raltegravir-naive infants enrolled in Cohort 2 are contained in the summary table:

**Table C. IMPAACT P1110 Cohort 2 Intensive PK Results[22]**

| 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<br>Met: 13<br>Below: 0 | 14.3 (43.3%) | Above: 8<br>Met: 14<br>Below: 1 |
| **Trough (ng/mL)** | 948 (64.2%) | Above: 25<br>Below: 0 | 176 (93.8%) | Above: 22<br>Below: 1 |
| **$C_{max}$ (ng/mL)** | 2,350 (35.0%) | Above: 0<br>Below: 25 | 2,850 (41.9%) | Above: 0<br>Below: 24 |
| **$T_{max}$ (ng/mL)** | 5.4 (57.5%) | N/A | 2.3 (67.1%) | N/A |
| **$T_{1/2}$ (hrs)** | 15.8 (174.8%) | N/A | 2.5 (33.5%) | N/A |

**PK Targets:** $AUC_{24}$, 12–40 mg*h/L; $AUC_{12}$, 6-20 mg*h/L

**Trough Concentrations:** >33 ng/mL

**Key to Acronyms:** AUC = area under the curve; $C_{max}$ = maximum concentration; PK = pharmacokinetic

Daily raltegravir was safe and well tolerated during the first 6 weeks of life. All GM protocol exposure targets were met. In some infants $AUC_{24}$ 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.

***Formulations***

The PK of raltegravir was compared in adult patients with HIV receiving 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 palatability was rated as poor.[23] In adult volunteers, the PK of raltegravir 800 mg taken once daily by chewing was compared to 2 doses of 400 mg 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.[24] 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 film-coated tablet based on a comparative study in healthy adult volunteers.[25] Interpatient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.[1,26] Because of the differences in the bioavailability of the film-coated tablets and each of the other formulations, the dosing recommendations for the film-coated tablets are different and not interchangeable with the chewable tablets or oral granules for suspension.

Palatability was evaluated as part of 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.[8,9]

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## Pharmacokinetic Enhancers

Cobicistat (COBI, TYBOST)

Ritonavir (RTV, Norvir)

# Cobicistat (COBI, TYBOST) (Last updated April 27, 2017; last reviewed April 27, 2017)

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 300 mg
- [*Genvoya*] Elvitegravir 150 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide 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 in adolescents and adults as a PK enhancer (boosting agent) of selected protease inhibitors (PIs) and the integrase inhibitor elvitegravir. Cobicistat is **not** interchangeable with ritonavir. See dosing information for specific PIs and elvitegravir 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)
- Stribild
- Evotaz
- Prezcobix
- Some Panel members consider that these agents may be appropriate in select children aged <18 years and weighing ≥35 kg; an expert in pediatric HIV infection should be consulted.

*Not FDA-Approved for Use in Children Aged <12 Years or Weighing <35 kg:*

- Genvoya
- Panel members consider that it may be appropriate to use Genvoya in children aged <12 years and weighing ≥35 kg; an expert in pediatric HIV infection should be consulted.

### Child/Adolescent and Weighing ≥35 kg

- Cobicistat 150 mg orally once daily as a component of Genvoya

### Adult (Aged ≥18 Years) Dose:

- Cobicistat must be administered as
  - The combination tablet Stribild or 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 combinations with TDF, monitor serum creatinine, urine protein, and urine glucose at baseline and every 3 to 6 months while on therapy (see Table 13i). 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 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-naive or treatment-experienced with virus susceptible to all ARV drug components of Stribild or Genvoya |
| 150 mg orally once daily | Atazanavir 300 mg (co-formulated as Evotaz or given as a separate drug) orally once daily plus other ARV drugs | Treatment-naive or treatment-experienced |
| 150 mg orally once daily | Darunavir 800 mg (co-formulated as Prezcobix or given as a separate drug) orally once daily plus other ARV drugs | Treatment-naive or treatment-experienced with no darunavir-associated resistance mutations |

- Cobicistat inhibits renal tubular secretion of creatinine, increasing the serum creatinine concentration (and decreasing estimated glomerular filtration rate) without decreasing actual glomerular function.

Dosing of Cobicistat 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 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- *Metabolism:* Cobicistat is an inhibitor of cytochrome P (CYP) 3A4 and a weak inhibitor of CYP2D6; in addition, cobicistat inhibits adenosine triphosphate (ATP)-dependent transporters BCRP and P-glycoprotein and the organic anion transporting polypeptides OAT1B1 and OAT1B3. By inhibiting P-glycoprotein 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 not containing cobicistat.[1,2] 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.
- Cobicistat and ritonavir are not interchangeable,[3] and administration with either atazanavir or darunavir may result in different drug interactions when used with other concomitant medications.

***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 antiretroviral drugs.

***Pediatric Use***

*Approval*

Cobicistat alone (as Tybost), or cobicistat coformulated with atazanavir (as Evotaz) or darunavir (as Prezcobix), 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 ≥12 years and body weight ≥35 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.[4]

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## Ritonavir (RTV, Norvir) (Last updated April 27, 2017; last reviewed April 27, 2017)

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

### Formulations

**Oral Solution (Contains 43% Alcohol by Volume):** 80 mg/mL

**Tablets:** 100 mg

### Dosing Recommendations

**Ritonavir as a Pharmacokinetic (PK) Enhancer:[a]**

- Ritonavir is used as a PK enhancer of other protease inhibitors (PIs). The recommended dose of ritonavir varies and is specific to the drug combination selected. See dosing information for specific PIs.

[a] Ritonavir has antiviral activity but is not used as an antiviral agent (see text).

### 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, Prezcobix, 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.
- To Increase Tolerability of Ritonavir Oral Solution in Children:
  - Mix solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream.
  - Before administration, give a child ice chips, a Popsicle, or spoonfuls of partially frozen orange or grape juice concentrate to dull the taste buds, or give peanut butter to coat the mouth.

- After administration, give a child strong-tasting foods such as maple syrup or 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) 3A4 and CYP2D6 inhibitor; CYP1A2, CYP2B6, CYP2C9, CYP2C19, and glucuronidation inducer.
- Dosing of ritonavir in patients with hepatic impairment: Ritonavir is primarily metabolized by the liver. No dosage 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.

***Drug Interactions*** (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://iasusa.org/sites/default/files/tam/october_november_2015.pdf#page=10)

- *Metabolism:* Ritonavir is extensively metabolized by and is one of the most potent inhibitors of hepatic cytochrome P450 3A (CYP3A). 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.[1]
- Avoid concomitant use of intranasal or inhaled fluticasone because of reports of adrenal insufficiency.[2] Use caution when prescribing ritonavir with other inhaled steroids; limited data suggest that beclomethasone may be a suitable alternative to fluticasone when an inhaled/intranasal corticosteroid is required for a patient who is taking ritonavir.[3,4]

***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.[5]

***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 antiretroviral 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 large pill burden with the tablets (adult dose is 6 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 CYP3A4 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 a PI co-formulation, lopinavir/ritonavir (LPV/r), are available (see individual PIs for more specific information).

*Toxicity*

Full-dose ritonavir has been shown to prolong the PR interval in a study of healthy adults who were given ritonavir at 400 mg twice daily.[5] Potentially life-threatening arrhythmias in premature newborn infants treated with LPV/r have been reported; the use of LPV/r **is not recommended** until the gestational age of 42 weeks.[6,7] 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 those with underlying structural heart disease, conduction system abnormalities, ischemic heart disease, or cardiomyopathy.

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# Appendix B: Acronyms (Last updated March 1, 2016; last reviewed April 27, 2017)

| Acronym/Abbreviation | Full Name |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| AE | adverse effect |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ATV | atazanavir |
| ATV/r | ritonavir-boosted atazanavir |
| AUC | area under the curve |
| AV | atrioventricular |
| BMD | bone mineral density |
| BMI | body mass index |
| BSA | body surface area |
| CBC | complete blood count |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| CK | creatine kinase |
| $C_{max}$ | maximum plasma concentration |
| $C_{min}$ | minimum plasma concentration |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| COBI | cobicistat |
| CrCl | creatinine clearance |
| CT | computed tomography |
| CVD | cardiovascular disease |
| CYP | cytochrome P |
| d4T | stavudine |

| | |
|---|---|
| ddI | didanosine |
| DM | diabetes mellitus |
| DMPA | depot medroxyprogesterone acetate |
| DOT | directly observed therapy |
| DRESS | drug rash with eosinophilia and systemic symptoms |
| DRV | darunavir |
| DRV/r | ritonavir-boosted darunavir |
| DXA | dual-energy x-ray absorptiometry |
| EBV | Epstein-Barr virus |
| EC | enteric-coated |
| ECG | electrocardiogram |
| EFV | efavirenz |
| EM | erythema multiforme |
| ETR | etravirine |
| EVG | elvitegravir |
| FDA | Food and Drug Administration |
| FLP | fasting lipid profile |
| FPG | fasting plasma glucose |
| FPV | fosamprenavir |
| FPV/r | ritonavir-boosted fosamprenavir |
| FTC | emtricitabine |
| FXB | François-Xavier Bagnoud Center |
| G6PD | glucose-6-phosphate dehydrogenase |
| G-CSF | granulocyte colony-stimulating factor |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| HAV | hepatitis A virus |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HDL-C | high-density lipoprotein cholesterol |
| Hgb | hemoglobin |
| HHS | U.S. Department of Health and Human Services |

| | |
|---|---|
| HIVMA | HIV Medicine Association |
| HRSA | Health Resources and Services Administration |
| HSR | hypersensitivity reaction |
| HSV | herpes simplex virus |
| IAS-USA | International Antiviral Society-USA |
| ICH | intracranial hemorrhage |
| IDSA | Infectious Diseases Society of America |
| IDV | indinavir |
| IMPAACT | International Maternal Pediatric Adolescent AIDS Clinical Trials Network |
| INH | isoniazid |
| INSTI | integrase strand transfer inhibitor |
| IQ | inhibitory quotient |
| IRIS | immune reconstitution inflammatory syndrome |
| IU | international units |
| IV | intravenous/intravenously |
| IVIG | intravenous immune globulin |
| LDL | low-density lipoprotein |
| LDL-C | low-density lipoprotein cholesterol |
| LFT | liver function test |
| LLQ | lower level of quantification |
| LPV | lopinavir |
| LPV/r | ritonavir-boosted lopinavir |
| MEMS | Medication Event Monitoring System |
| MVC | maraviroc |
| NASBA | nucleic acid sequence-based amplification |
| NAT | nucleic acid test |
| NFV | nelfinavir |
| NHLBI | National Heart, Lung, and Blood Institute |
| NIH | National Institutes of Health |
| NNRTI | non-nucleoside reverse transcriptase inhibitor/non-nucleoside analogue reverse transcriptase inhibitor |
| non-HDL-C | non-high-density lipoprotein cholesterol |
| NRTI | nucleoside reverse transcriptase inhibitor/nucleoside analogue reverse transcriptase inhibitor |

| | |
|---|---|
| NVP | nevirapine |
| OARAC | Office of AIDS Research Advisory Council |
| OGTT | oral glucose tolerance test |
| OI | opportunistic infection |
| PCP | *Pneumocystis jiroveci* pneumonia |
| PCR | polymerase chain reaction |
| PG | plasma glucose |
| Pgp | p-glycoprotein |
| PI | protease inhibitor |
| PK | pharmacokinetic |
| PPI | proton-pump inhibitor |
| PR | protease |
| PUFA | polyunsaturated fatty acid |
| PY | patient years |
| RAL | raltegravir |
| RBV | ribavirin |
| RPG | random plasma glucose |
| RPV | rilpivirine |
| RT | reverse transcriptase |
| RTV | ritonavir |
| SJS | Stevens-Johnson syndrome |
| SMR | sexual maturity rating |
| SQ | subcutaneous |
| SQV | saquinavir |
| T-20 | enfuvirtide |
| TAF | tenofovir alafenamide |
| TB | tuberculosis |
| TC | total cholesterol |
| TDF | tenofovir disoproxil fumarate |
| TDM | therapeutic drug monitoring |
| TEN | toxic epidermal necrolysis |
| TG | triglyceride |
| THAM | tris–hydroxymethyl-aminomethane |

| | |
|---|---|
| TMP-SMX | trimethoprim sulfamethoxazole |
| TPV | tipranavir |
| TPV/r | ritonavir-boosted tipranavir |
| UGT1A1 | uridine diphosphate glucoronosyltransferase |
| ULN | upper limit of normal |
| USPHS | U.S. Public Health Service |
| WHO | World Health Organization |
| ZDV | zidovudine |

# Appendix C: Supplemental Information (Last updated February 12, 2014; last reviewed February 12, 2014)

**Table A. Likelihood of Developing AIDS or Death Within 12 Months, by Age and CD4 T-Cell Percentage or $Log_{10}$ HIV-1 RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

| | CD4 Percentage | | | | $Log_{10}$ HIV RNA Copy Number | | |
|---|---|---|---|---|---|---|---|
| **Age** | **10%** | **20%** | **25%** | **30%** | **6.0** | **5.0** | **4.0** |
| **Percent Mortality (95% Confidence Interval)** | | | | | | | |
| **6 Months** | 28.7 | 12.4 | 8.5 | 6.4 | 9.7 | 4.1 | 2.7 |
| **1 Year** | 19.5 | 6.8 | 4.5 | 3.3 | 8.8 | 3.1 | 1.7 |
| **2 Years** | 11.7 | 3.1 | 2.0 | 1.5 | 8.2 | 2.5 | 1.1 |
| **5 Years** | 4.9 | 0.9 | 0.6 | 0.5 | 7.8 | 2.1 | 0.7 |
| **10 Years** | 2.1 | 0.3 | 0.2 | 0.2 | 7.7 | 2.0 | 0.6 |
| **Percent Developing AIDS (95% Confidence Interval)** | | | | | | | |
| **6 Months** | 51.4 | 31.2 | 24.9 | 20.5 | 23.7 | 13.6 | 10.9 |
| **1 Year** | 40.5 | 20.9 | 15.9 | 12.8 | 20.9 | 10.5 | 7.8 |
| **2 Years** | 28.6 | 12.0 | 8.8 | 7.2 | 18.8 | 8.1 | 5.3 |
| **5 Years** | 14.7 | 4.7 | 3.7 | 3.1 | 17.0 | 6.0 | 3.2 |
| **10 Years** | 7.4 | 2.2 | 1.9 | 1.8 | 16.2 | 5.1 | 2.2 |

**Note:** Table modified from: HIV Paediatric Prognostic Markers Collaborative Study Group. *Lancet*. 2003;362:1605-1611.

**Table B. Death and AIDS/Death Rate per 100 Person-Years by Current Absolute CD4 Cell Count and Age in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy (HIV Paediatric Prognostic Markers Collaborative Study) and Adult Seroconverters (CASCADE Study)**

| | Absolute CD4 Cell Count (cells/$mm^3$) | | | | | |
|---|---|---|---|---|---|---|
| **Age (Years)** | **<50** | **50–99** | **100–199** | **200–349** | **350–499** | **500+** |
| **Rate of Death Per 100 Patient-Years** | | | | | | |
| **0–4** | 59.3 | 39.6 | 25.4 | 11.1 | 10.0 | 3.5 |
| **5–14** | 28.9 | 11.8 | 4.3 | 0.89 | 0.00 | 0.00 |
| **15–24** | 34.7 | 6.1 | 1.1 | 0.71 | 0.58 | 0.65 |
| **25–34** | 47.7 | 10.8 | 3.7 | 1.1 | 0.38 | 0.22 |
| **35–44** | 58.8 | 15.6 | 4.5 | 0.92 | 0.74 | 0.85 |
| **45–54** | 66.0 | 18.8 | 7.7 | 1.8 | 1.3 | 0.86 |
| **55+** | 91.3 | 21.4 | 17.6 | 3.8 | 2.5 | 0.91 |
| **Rate of AIDS or Death per 100 Patient-Years** | | | | | | |
| **0–4** | 82.4 | 83.2 | 57.3 | 21.4 | 20.7 | 14.5 |
| **5–14** | 64.3 | 19.6 | 16.0 | 6.1 | 4.4 | 3.5 |
| **15–24** | 61.7 | 30.2 | 5.9 | 2.6 | 1.8 | 1.2 |
| **25–34** | 93.2 | 57.6 | 19.3 | 6.1 | 2.3 | 1.1 |
| **35–44** | 88.1 | 58.7 | 25.5 | 6.6 | 4.0 | 1.9 |
| **45–54** | 129.1 | 56.2 | 24.7 | 7.7 | 3.1 | 2.7 |
| **55+** | 157.9 | 42.5 | 30.0 | 10.0 | 5.1 | 1.8 |

**Note:** Table modified from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis*. 2008;197:398-404.

**Table C. Association of Baseline Human Immunodeficiency Virus (HIV) RNA Copy Number and CD4 T-Cell Percentage with Long-Term Risk of Death in HIV-Infected Children[a]**

| Baseline HIV RNA[c] (Copies/mL) Baseline CD4 Percentage | No. Patients[d] | Deaths[b] Number | Deaths[b] Percentage |
|---|---|---|---|
| **≤100,000** | | | |
| ≥15% | 103 | 15 | (15%) |
| <15% | 24 | 15 | (63%) |
| **>100,000** | | | |
| ≥15% | 89 | 32 | (36%) |
| <15% | 36 | 29 | (81%) |

[a] Data from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial.

[b] Mean follow-up: 5.1 years.

[c] Tested by NASBA® assay (manufactured by Organon Teknika, Durham, North Carolina) on frozen stored serum.

[d] Mean age: 3.4 years.

Source: Mofenson LM, Korelitz J, Meyer WA, et al. The relationship between serum human immunodeficiency virus type 1 (HIV-1) RNA level, CD4 lymphocyte percent, and long-term mortality risk in HIV-1-infected children. *J Infect Dis*. 1997;175(5):1029–1038.

**Figure A. Estimated Probability of AIDS Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

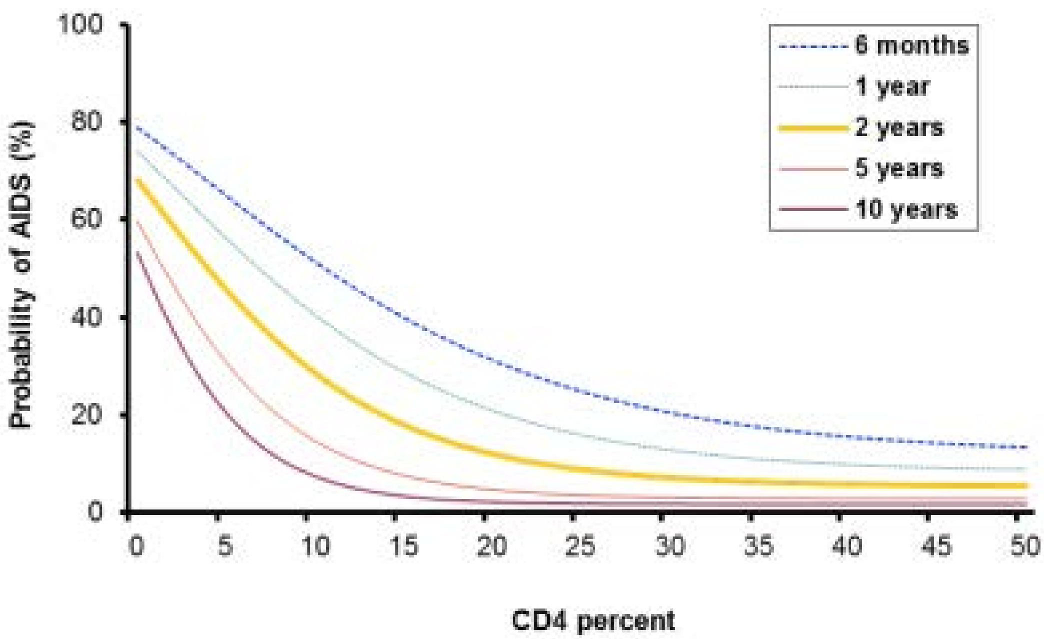


Figure modified from *Lancet* 2003;362:1605-1611

**Figure B. Estimated Probability of Death Within 12 Months by Age and CD4 Percentage in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

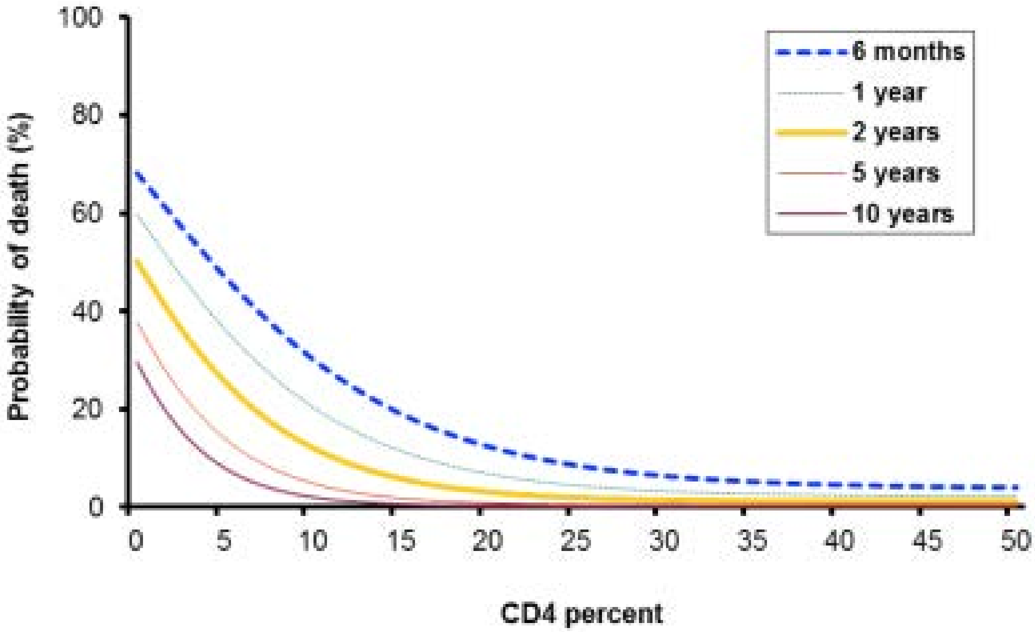


Figure modified from *Lancet* 2003;362:1605-1611

**Figure C. Death Rate per 100 Person-Years in HIV-Infected Children Aged 5 Years or Older in the HIV Paediatric Prognostic Marker Collaborative Study and HIV-Infected Seroconverting Adults from the CASCADE Study***

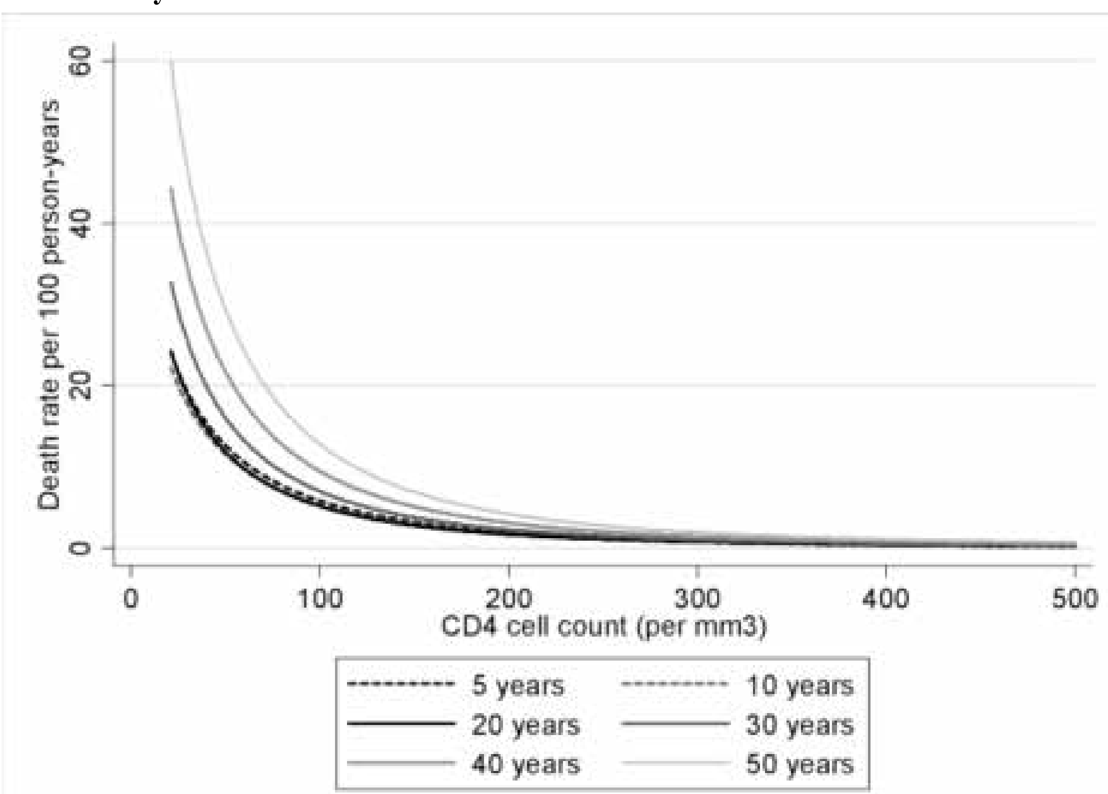


Figure modifed from: HIV Paediatric Prognostic Markers Collaborative Study and the CASCADE Collaboration. *J Infect Dis*. 2008;197:398-404.

**Figure D. Estimated Probability of AIDS Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

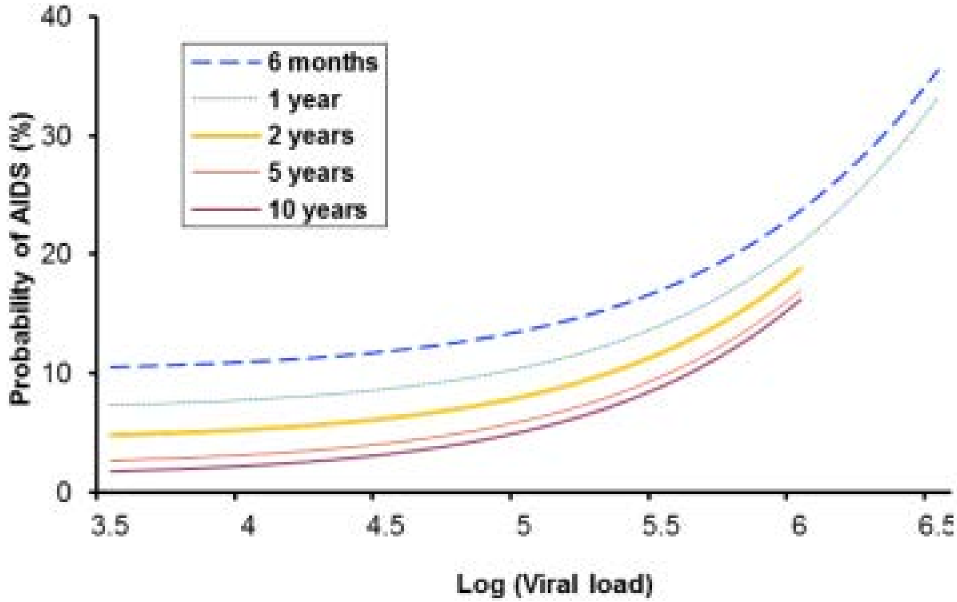


Figure modified from *Lancet* 2003;362:1605-1611

**Figure E. Estimated Probability of Death Within 12 Months of Age and HIV RNA Copy Number in HIV-Infected Children Receiving No Therapy or Zidovudine Monotherapy**

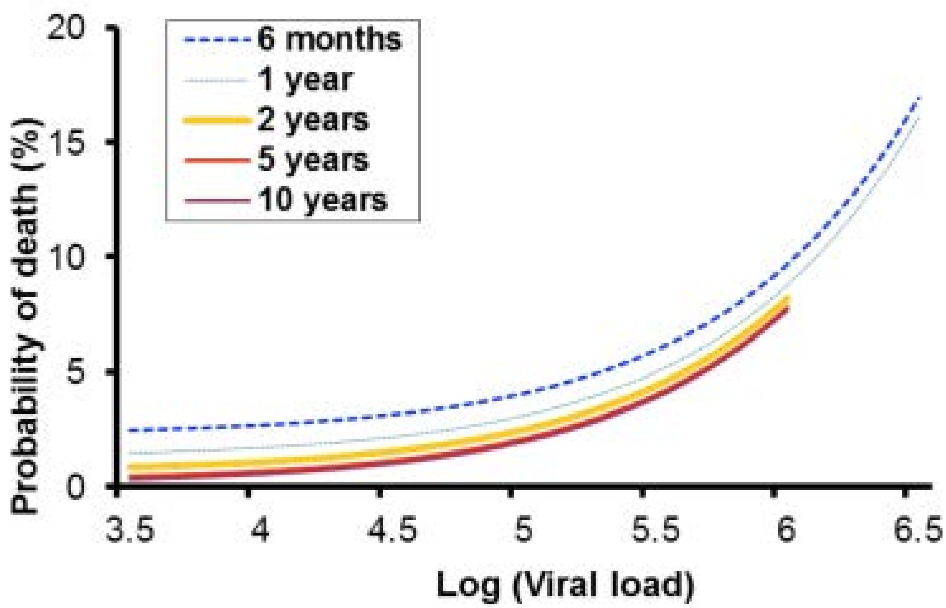


Figure modified from *Lancet* 2003;362:1605-1611